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Historical and Contemporary Aspects of Communicable Disease Control

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Contents

COVER: Block of 1969 stamps issued by the Republic of Mali in honor of the smallpox vaccination campaign. The stamps are provided by Pascal J. Imperato, whose article begins on page 61 of this issue.

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An Introduction

Historical and Contemporary Aspects of Communicable Disease Control

Pascal James Imperato, *Guest Editor*

There is a renewed interest in communicable diseases in the United States as we approach the close of the twentieth century. That interest may seem paradoxical since this is the century in which the major communicable diseases were believed conquered in this country through a combination of improved living standards, sanitary measures, vaccines, and antibiotics. So dramatic was the decline in morbidity and mortality from such major communicable diseases as polio, measles, and rubella, that by the early 1970s the New York City Department of Health had difficulty recruiting a director for its Bureau of Communicable Disease Control.[1] Yet this was the bureau that only a few years before had investigated major epidemics made famous by Berton Roueche in his book *Eleven Blue Men*.[2]

There were several reasons why communicable disease control had fallen to a lower priority in public health. Dramatic reductions in the morbidity and mortality of those diseases generated excessive confidence in the abilities of vaccines and antibiotics alone to control them. Other public health priorities—including lead poisoning and the heroin epidemic—moved to center stage and received significant levels of both federal and state funding. There was a failure to recognize that changing demographic patterns due to immigration from disease-endemic Third World countries would soon introduce large numbers of infected individuals, as in the case of tuberculosis. Regrettably, public policy makers and legislators cut funding for immunization programs, failing to realize that inadequate access to them for poor inner-city and rural children would create large pools of susceptibles capable of sustaining new epidemics and outbreaks. Finally, there was little understanding that social behaviors could start and sustain epidemics. The role of crack cocaine in generating the national syphilis epidemic of the late 1980s and early 1990s is a recent example of the powerful influence of a social determinant on disease morbidity.[3]

For most of the 1970s, public health departments in the United States provided steady but back-burner support for communicable disease control activities. The 1976

outbreak of Legionnaires' disease in Philadelphia caused some public health leaders to rethink their spending priorities. Most, however, viewed the Philadelphia and subsequent outbreaks of the disease as unusual events that did not require a shift in resource allocation. That complacency was reinforced when the predicted 1976 Swine Flu epidemic did not occur.[4] Yet from a certain perspective, the outbreaks of Legionnaires' disease of the 1970s and cases of toxic shock syndrome in the early 1980s put public health departments on alert to the reality that they could no longer take communicable disease control for granted. Despite the disappearance of naturally transmitted smallpox in 1977 and the development of more effective vaccines and antibiotics, prescient public health specialists and scientists recognized that newer pathogens might emerge from man's manipulation of his environment, and that existing pathogens could soon prove to be resistant to known prophylactic and therapeutic agents.

By the mid-1980s, after a lapse of almost two decades, communicable disease control units were once again at the center of public health departments. This dramatic shift was brought about by the epidemic of acquired immunodeficiency syndrome (AIDS) in the early 1980s. As federal and state funding improved, public health departments rebuilt their communicable disease control capabilities around AIDS. Infections such as tuberculosis and syphilis, which reappeared in epidemic form in the late 1980s, sustained their strong commitment to communicable disease control. Finally, emerging pathogens, notably the Ebola virus, have demonstrated that the future of communicable disease control contains many unknowns.

The emerging pathogens of the 1990s have caused a drastic change in how we now view

This first-day cover for a 50 franc stamp, issued November 10, 1969, commemorated the smallpox eradication/measles control program in Mali.

communicable disease control. The excessive confidence of the 1970s has given way to a greater realization of the complexities of human/pathogen interactions. There has also been a commitment of resources. That understanding and commitment are fueled not only by the insights of scientists but also by the concerns of the American public, who have learned that these pathogens are often fatal, defying easy solution through the use of vaccines and drugs. They both fascinate and frighten, and often appear because we alter and disrupt the delicate balances between them, us, and the environment we share.[5]

World population growth has given rise to human encroachment on what were once the wild refuges of many pathogens. In those remote forested environments, viruses such as Ebola have reached a state of equilibrium with natural hosts over many millennia. Once transported from that balanced environment, the viruses cause lethal epidemics as they enter a human population with which they have had little or no contact.

Man is not only coming into contact with new viruses but also transporting old ones

The Ped-O-Jet automatic jet injector being used to administer measles vaccine, San, Mali, 1968

to different locations. We facilitate the spread of epidemics by manipulating our indoor environments and the food we eat. Our excessive and often unnecessary use of antibiotics has given rise to resistant strains of bacteria. The result has been dramatic rises in deaths from pneumonia and septicemia, often among hospitalized elderly patients. In response to the growing threat of infectious diseases, the *Journal of the American Medical Association* and thirty-five other medical journals joined together on January 16, 1996, in a concerted call for increased efforts against these diseases.[6] The editors simultaneously published a total of 242 articles on the subject to emphasize its importance. One of the most sobering statistics to emerge from those studies is that, exclusive of AIDS, infectious disease mortality rose by 22 percent in the United States between 1980 and 1992.[7]

If the first eight decades of the twentieth century were marked by continued success in the control of communicable diseases, the last two decades have brought us to the sobering frontier of emerging and reemerging infections. We now recognize that we will have to deal continuously with newer epidemics due to our disruption of the environment, as well as with older ones that emerge because of social, technical, and behavioral determinants.

The essays in this issue of *Caduceus* demonstrate both the complexities of several pathogens and the challenges inherent in attempts to control the epidemics they cause. In addition, John S. Marr and Curtis D. Malloy present a new and interesting unitarian hypothesis concerning the ten plagues of ancient Egypt. They use a modern epidemiologic approach to analyze these plagues, discuss previous scholarly conclusions, and use the entire corpus of available data to formulate their new hypothesis. Their conclusions will certainly not be the last on this approximately 3,500-year-old story. They will however, stimulate further reflection and discussion, proving once again the wisdom of the ancient Greeks, who observed: "There is always something new out of Africa."[8]

John P. Craig discusses the fascinating story of the Seventh Cholera Pandemic, which began in 1961. His essay presents intriguing details about the epidemiology, bacteriology, and immunology of the *Vibrio cholerae*. He shows how recent advances in oral and intravenous fluid and electrolyte replacement therapy, as well as greater expertise on the part of medical personnel, have reduced mortality to less than one percent. This is a remarkable twentieth-century accomplishment for a disease that was once invariably fatal for half of those who contracted it. Yet, as Dr. Craig notes, cholera is primarily controlled today not by vaccination or by breaking the chain of transmission but by treating people after they have contracted it.

Tuberculosis, once known as the "white plague," was a major cause of morbidity and mortality in the United States in the early part of this century.[9] It caused enormous social disruption and great economic hardships as families were broken up in the inter-

ests of isolating victims in sanitoria. Isolation, rest, fresh air, and surgical procedures were all that medicine had to offer in terms of treatment. A vast system of state-operated sanitoria filled with tuberculosis patients was in existence until the 1940s, when antituberculosis drugs became widely available. Most of these specialized hospitals were closed by the 1960s and 1970s, vivid testimony to the assumed conquest of yet another communicable disease.[10] Yet was the disease really controlled? As Mahfouz H. Zaki and Mary E. Hibberd describe in their essay on tuberculosis, early assumptions about eradication were quickly proven wrong. As disease prevalence declined in this country, however, federal funding for tuberculosis control programs was dramatically reduced. Such programs were given an increasingly lower priority in local health departments, based on the assumption that the disease was well under control. During the 1980s, the incidence of tuberculosis suddenly surged in the United States due to imported infections among recent immigrants and AIDS-associated disease.

As Drs. Zaki and Hibberd describe, there are many newer and difficult challenges posed by this reemerged infection. Among them are multiple drug-resistant strains and the growth of patient noncompliance with drug treatment. Zaki and Hibberd detail the enormous financial costs of controlling the resurgent tuberculosis epidemic. They also make the cogent observation that relaxing control measures and reducing funding for a disease whose incidence is declining is a serious public health policy error.

The fourth essay in this issue contrasts the control strategies and outcomes for smallpox and measles in the West African country of Mali. A focused country study, it serves to illustrate a number of the issues and problems that confronted many of the other eighteen West and Central African countries that participated in a multiyear effort to eradicate smallpox and control measles.

The eradication of smallpox stands as one the great public health achievements of the twentieth century. The success of the eradication effort in West and Central Africa was in large measure due to the dedication and expertise of American personnel assigned to individual countries. Backed by a committed leadership staff at the Centers for Disease Control in Atlanta, these young physicians and operations officers left for Africa full of enthusiasm, hope, and even trepidation. Their determination had been galvanized over a period of several months in Atlanta, where they were trained not only to diagnose smallpox and investigate epidemics but also to speak French and repair the engines of Dodge trucks.

The field staff of courageous young Americans was fortunate in having an experienced and accomplished physician as their leader. George Ignatius Lythcott never wavered in his belief that smallpox could be eradicated. As regional director for the West and Central African Smallpox Eradication/Measles Control Program, he continuously pursued that goal. More important, he provided his staff with the encouragement, support, and counsel needed to overcome enormous odds. In so doing, he helped create the ultimate triumph of eradicating a disease.[11]

The closing years of the twentieth century are a fitting time to examine different aspects of communicable disease control. For this is the century in which historic advances took place in the prevention, control, and treatment of many diseases. Antibiotics were developed and have saved millions of lives. Effective vaccines for preventing the killer

lives. Effective vaccines for preventing the killer diseases of childhood have allowed youngsters all over the world to reach adulthood. Improved living standards and sanitation have helped to interrupt disease transmission, and science has found the means to treat even viruses.

This is also the century, however, in which we came to realize that combinations of social, technical, and behavioral determinants greatly influence the life histories of communicable diseases. Emerging and reemerging epidemics—as well as antibiotic resistance—have their origins in human actions. Both scientists and the public now know that future successes against these diseases will not be achieved through a reliance on drugs and vaccines alone. The essays in this issue of *Caduceus* address some of these issues, and bring the lessons of history to bear upon present and future efforts at communicable disease control.

♦

Notes

1. Pascal James Imperato, *Medical Detective* (New York: Richard Marek Publishers, 1979), 163–64.

2. Berton Roueche, *Eleven Blue Men and Other Narratives of Medical Detection* (Boston: Little Brown & Co., 1953).

3. R. T. Rolfs and G. P. Schmid, "The United States syphilis epidemic: Reason for optimism (at least for the moment)," *New York State Journal of Medicine* 91 (1991): 522–23.

4. Richard E. Neustadt and Harvey V. Fineberg, *The Swine Flu Affair. Decision-Making on a Slippery Disease* (Washington, D.C.: U.S. Department of Health, Education, and Welfare, 1978).

5. Emerging pathogens currently attract much popular attention. They have been the subject of popular books (e.g., Laurie Garrett, *The Coming Plague: Newly Emerging Diseases in a World out of Balance* [New York: Farrar, Straus and Giroux, 1994]), a Hollywood film ("Outbreak"), front-page news stories, and prime-time television coverage.

6. D. A. Goldmann, R. A. Weinstein, R. P. Wenzel, et al., "Consensus Statement: Strategies to Prevent and Control the Emergence and Spread of Antimicrobial-resistant Micro-organisms in Hospitals: A Challenge to Hospital Leadership," *JAMA* 275 (1996): 234–40; J. A. Patz, P. R. Epstein, T. A. Burke, et al. "Global Climate Change and Emerging Infectious Diseases," *JAMA* 275 (1996): 217–23; J. Lederberg, "Infection Emergent," *JAMA* 275 (1996): 243–45; M. A. Winker and A. Flanagin, "Infectious Diseases: A Global Approach to a Global Problem," *JAMA* 275 (1996): 245–46.

7. "Doctors Tell of International Resurgence in a Variety of Infectious Diseases," *New York Times*, Jan. 17, 1966, A16; R. W. Pinner, S. M. Teutsch, L. Simonsen, et al., "Trends in Infectious Diseases Mortality in the United States," *JAMA* 275 (1996): 189–93.

8. Pliny the Elder (23–79), a Roman scholar, popularized the Greek proverb in Latin as "Ex Africa semper aliquid novi."

9. R. J. Dubos, "Biologic and Epidemiological Aspects of Tuberculosis," *American Review of Tuberculosis* 68 (1953): 1–8.

10. K. W. Wright, J. Monroe, and F. Beck, "A History of the Ray Brook State Tuberculosis Hospital," *New York State Journal of Medicine* 90 (1990): 406–13.

11. Lythcott later became associate dean for urban and community affairs at the Columbia University College of Physicians and Surgeons, associate vice-chancellor for academic affairs at the University of Wisconsin, and in 1977 was appointed by President Jimmy Carter as administrator of the health services administration in the Department of Health and Human Services. He then served as dean of the City University of New York's Sophie Davis School of Biomedical Education, and later as assistant commissioner in the New York City Department of Health. He died at his home on Martha's Vineyard on Oct. 7, 1995. See Wolfgang Saxon, "George Lythcott, 77, Pediatrician, Dean and Health Official," *New York Times*, Oct. 11, 1995, B8.

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An Epidemiologic Analysis of the Ten Plagues of Egypt

John S. Marr and Curtis D. Malloy

The Ten Plagues of Egypt described in the Book of Exodus are the first example in a historical written record of what today might be described as "emerging infections." Causes and interpretations of the Ten Plagues have fascinated theologians, historians, Egyptologists, musical composers, scientists, and physicians for centuries. More recently other health professionals in various disciplines—including epidemiology, epizootiology, entomology, microbiology, and toxicology—have postulated probable causes for one or more of the plagues. In recent years reinterpretations of ancient texts and new information about environmental factors and disease causation have allowed unique interpretations of that series of early public health catastrophes. Yet despite centuries of study, fundamental questions remain.[1]

Were the Ten Plagues historical events, or perhaps only a collection of religious archetypal stories or myths? If the plagues did occur, why were there no specific citations to them in ancient Egyptian literature? If Egyptological research suggests some semblance of their occurrence, who might best "fit" as the candidate for pharaoh presiding over the plagues' occurrence? If a specific pharaoh can be posited (and satisfactorily reconciled within the more accepted talmudic and biblical chronological timeframes), when and where in time and place (theological and Egyptological) would the plagues under his reign and the ensuing Exodus have occurred? After those questions have been addressed, one is in a better position to offer a scientific interpretation to these questions: What were the causes of each of the Ten Plagues? How did they occur?

This paper will attempt to integrate biblical, historical, and Egyptological data to support a logical conjecture for the specific time, place, and pharaoh. Our conclusions follow the traditional tenets of epidemiologic investigation, the first of which is to answer the question, "Was there an epidemic?" That will be followed by corollary questions of when, where, and who might have been affected—the time-place-person questions of descriptive epidemiology. We then address specific explanations for each of the Ten Plagues, attempting to answer the "how" and "why" of analytical epidemiology.

Previous authors have postulated many explanations of the plagues—theological, supernatural, quasi-scientific, and scientific. We will address those extensive and good works, using Occam's razor as needed to reduce discordant explanations to the simplest and most logical. We then propose that the first nine plagues built upon each of the preceding plagues, and precipitated the final, most devastating plague, which culminated

in finally having the pharaoh agree to Moses' demand to "let my people go" (Exodus 5:1).[2]

Did the Ten Plagues Occur?

The epidemiologic analogue to the above question is "Was there an epidemic?" If the answer is no, the investigation is terminated. There is some evidence, however, separate from the original talmudic and biblical accounts, that the plagues did occur. Immanuel Velikovsky has cited passages from the *Admonitions of Ipuwer* (as translated in 1909 by Sir Alan H. Gardner), an ancient Egyptian papyrus, which substantiates that a series of catastrophes did occur at the end of the Middle Kingdom.[3] One of the earliest and most complete analysis of possible causes of the plagues was offered by Greta Hort, who based her theory on passages from the papyrus.[4]

Who, Where, and When?

There is little if any secular information to substantiate the historicity of the Exodus account. Some Egyptologists consider the Bible as story, not as history, noting that half a millennium or more had passed between the time of those events and the time of the first known written Hebrew literature. A strictly historical analysis would reveal that if the plagues and the Exodus did occur, they must have transpired before 1200 B.C.E., when the so-called "Israel" stela of the Pharaoh Merneptah described a people—not a country—called "Israel" that had already reached Canaan.

Furthermore, some have criticized utilizing the Ipuwer papyrus to substantiate the Exodus account, stating Ipuwer simply provides a contrast to the transition from a previously chaotic environment to the subsequent reign of a just and capable ruler.

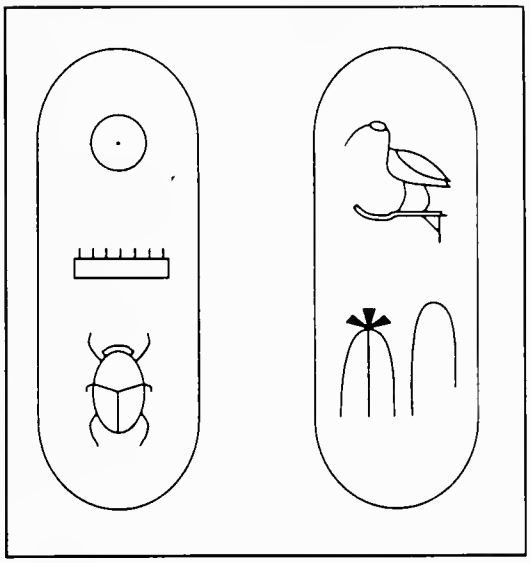
Many scholars who believe that the plagues actually occurred nevertheless disagree on the identity of the reigning pharaoh (and therefore on the likely years). Hort wisely ignores the question. Donovan A. Courville, after considerable debate, was unable to make a determination. Citing first century A.D. Jewish theologian Josephus as an authority, Cecil B. DeMille chose Ramesses II for his cinematic rendition *The Ten Commandments*. In 1981 Biblical scholar Werner Keller also reasoned that Ramesses II was the pharaoh. H. M. D. Hoyte, on the other hand, citing John J. Bimson, concluded in 1993 that the pharaoh was Thutmose III. Velikovsky appears to concur with Hort, although his candidate is not specified. He identifies a "Taui Thom the last king of the Middle Kingdom. He is the Tau Timaeus (Tutimaeus of Manetho)." Egyptologists today prefer the spelling of Thutmose for the various New Kingdom, 18th Dynasty rulers. Independent of various spellings, however, all four Thutmoses (I–IV) reigned well after the Hyksos, who were posited by Velikovsky.[5]

A definitive identification of the pharaoh is of some interest since the two (or more) postulated pharaohs span different time periods, varying slightly, depending on the source of dating: Ramesses II (1290–1224 B.C.E.); Thutmose I (1504–1492 B.C.E.); Thutmose II (1492–1479 B.C.E.); Thutmose III (1479–1425 B.C.E.); and Thutmose IV (1401–1391 B.C.E.). For Velikovsky that is of greater importance, as he ties the plagues and fiery pillar and parting of the Red Sea to other contemporary Old and New World historical accounts. His overall explanation is a

series of major climatological disasters precipitated by a comet and coinciding with the Hyksos invasion. Unfortunately, the Hyksos period (1640–1532 B.C.E.) does not coincide with any of the four Thutmoses.[6]

Hoyte suggested that the Ten Plagues took place under Thutmose III (1479–1425 B.C.E.) over an eleven-month span, beginning in July–August and lasting through April–May of the following year. Neither the two pharaohs suggested by most scholars—Thutmose III or Ramesses II—nor the duration of ten months within which those plagues may have taken place, are incompatible with the selected notations of the Ipuwer papyrus.

Scholars do agree that the ancient city of Memphis (today, Mit Rahina), located at the mouth of the Nile delta, was the residence of late Middle Kingdom and early New Kingdom pharaohs. A consensus supports that the land of Goshen was somewhere northeast of Memphis, near the ancient (now lost) city of Heliopolis, a few miles north of present-day Cairo. Heliopolis was referred to in the Bible as "On, Aven, and Beth-Shemesh." Hort proposed that Goshen lay some fifty miles northeast of Heliopolis, in the Wadi Tumilat near present-day Tell el-Maskhuta, a river valley that once connected the Nile to the northern extension of the Red Sea. If Goshen existed today, it would be about fifty miles northeast of present-day Cairo, less than one hundred miles from what is today known as the Gaza strip. The Red Sea is viewed by most historians as a mistranslation of the reed sea, a marshy extension of water extending from the Red Sea toward southwest Gaza. Indeed, a fast, primarily easterly exit from Memphis (29.8°), through Heliopolis (30.1°) and Goshen (Wadi Tumilat, 30.8°) would be well above the northernmost extension of the Red Sea (30.0°).[7]



Seal of Thutmose III

(Reproduced with permission from John Baines and Jaromir Malek, Atlas of Ancient Egypt *[New York: Facts on File, 1989])*

Interpretations of the Ten Plagues of Egypt

Interpretations of what the Ten Plagues might have been can be grouped into two categories: theological and scientific. The former group explores not only alternative translations of the original Hebrew and Aramaic texts but also secondary biblical interpretations. Scientific writers offer explanations for either a specific plague, a selected subset of plagues, or all ten of them. They further propose either separate explanations for each plague or procrustean theories to identify a single common factor or condition. We have chosen to discuss the plagues in pairings of successive twos, which we believe is the simplest way of discussing and building toward a logical and unified conclusion for the final, devastating plague.[8] For a summary of all interpretations, see pages 12–13.

First and Second Plagues—Fresh Waters Turn to Blood and Frogs

Prior to the germ theory, the only explanation posited for the cause of the first plague was an unknown noncontagionist

theory of "contamination" that could cause an extensive fish kill. After the advent of the germ theory, more specific infectious and noninfectious causes have been postulated. Silt remained an early candidate as the cause of a reddish Nile; later, that explanation was refined to a specific silt known as "marl," originating from Ethiopia and carried by a cresting Blue Nile. Velikovsky's more recent proposal was that cometary red dust caused the Nile to turn color.[9]

Recent explanations for the red-colored waters have favored protozoan, zooplankton, dinoflagellates, and both salt- and freshwater algal (phytoplankton) blooms. All of those blooms—plant, fungal, or protozoan—deoxygenate water and produce noxious toxins for both fish and frogs. Without predator fish, frogs could initially breed freely in both ponds and the Nile; in time they would overpopulate the river, eventually escaping the anoxic, toxic, and putrefying environment by migrating to land, hence to die and decompose along with the fish. The Nile and adjacent land would thus become fouled, and the waters dangerous to drink or bathe in.

P. A. Tester, citing the Exodus account, noted that while fewer than fifty out of approximately five thousand known phytoplankton species are toxic, those that possess toxins can be dangerous to aquatic life. E. C. D. Todd, referring to historic and prehistoric data, cites nearly two dozen examples of specific phytoplanktons causing various outbreaks throughout the world. Wayne W. Carmichael listed diseases associated with freshwater blue-green algae. JoAnn M. Burkholder described the dinoflagellate *Pfiesteria piscimorte*, which was found in estuary waters and, as the species name implies, was capable of killing fish. Neither an unstated contamination, cometary dust, nor silt would by itself explain all of the phenomena described above. In addition, the Nile, its tributary waters, well water, and other bodies of standing water were fresh. Most of the above-mentioned aquatic, phytotoxic blooms occur in salt or brackish water, with the exception of the recent discovery of freshwater blooms.[10]

We conclude that a freshwater dinoflagellate biomass bloom, as described by Carmichael and Burkholder, was responsible for the change in the color of the Nile, the death of fish, and the subsequent population explosion among frogs.

The death of fish—"an important source of protein and minerals" for the ancient Egyptian, was more than an inconvenience. It was the first of many nutritional compromises caused by ensuing plagues to be inflicted on the Egyptian Empire, culminating in the last plague. The eventual death of frogs also removed an important health agent, for frogs were the natural enemy of certain biting insects that were otherwise free to multiply unhindered.[11]

Third and Fourth Plagues—Lice and the Swarm of Flies

The first mention of two of the three members of the Class Insecta (*Hexapoda*) is of particular interest to entomologists (the second mention occurs with the locusts of the seventh plague). Richard L. Brown has noted that any identification of an insect by either order or genus in the Book of Exodus predates the first taxonomic attempts by Aristotle to classify insects (or arthropods) by nearly one thousand years. Thus, any arthropod may be considered a putative vector, including the members of the Class Arachnida—soft ticks, hard ticks, scorpions, spiders, and mites. All such arthropods abounded in Egypt.[12]

The original Hebraic term for "lice" is most often translated as "vermin." That term, as such, is commonly construed as an arthropod skin infestation, not as flying insects. The term also implies that the multiple offenders could be visibly recognized. Thus, the otherwise ingenious conclusion by J. Korzets that the cause of the third plague "itch" was due to the microscopic scabies mite (*Sarcoptes scabiei*) is probably incorrect, although David J. Sencer notes that the chronic allergic sequela of that infestation, "beggars' itch," is an alternative explanation. Of the three human body lice known today (*Pediculus corporis humanis, P. capitis humanis*, and *Pthirus pubis*), none fulfill the description of the macroscopic infestation "on man and beast," since those lousy candidates are species-specific, and do not infest nonhuman hosts, as the text clearly states.[13]

Alternative explanations are such indiscriminate biters as the soft tick (*Orthinodoris moubati*), hard tick (*Boophilus annulatus*), and maggot infestation or myiasis (e.g., *Dermatobia hominis*) found in North Africa. Although entomologically correct for Egypt, all of those dermatological infestations are too macroscopic to warrant usage of the term "vermin." And, like lice, none have the capability of flying.

Of flying insects resident in Egypt, recent findings that *Simulian* species of blackflies transmitting onchocerciasis (river blindness) in many areas of eastern Africa (including the Sudan) offers another explanation. The dermatosis caused by those flies is singularly characterized by intense itching. Even if blackflies were candidates for the "lice," however, the vector is too large and recognizable to be called vermin, and the pruritus induced by an allergic reaction to the death of *O. volvulus* microfilaria takes months or years to appear.

Hoyte suggests an alternative to the Hebraic translation of "chinnim"—the Greek "sciniphes," or mosquito/gnat. More than forty species of mosquito capable of transmitting disease have been cataloged in Egypt; the most abundant genera of mosquito, in decreasing order, are *Anopheles, Culex, Aedes, Culiseta*, and *Uranotaenia*. Mosquitoes are relatively large and easily recognized. Nevertheless, Hoyte preferred the mosquito *Culex antennatus* as the most likely explanation for "lice." By so doing, he dismissed the midge and sandfly as both the cause of the infestation and as a possible vector for subsequent plagues.[14]

The midge, a lay term that includes *Culicoides* species (also known as gnats, "no-see-ums" and "punkies") are nematocerous flies whose larvae and pupae live in moist soil. They are small and bloodsucking, thus better fulfilling the near-microscopic description of "lice"; furthermore, they may appear to originate in "dust" because their pupae develop and eventually fly out from what would appear as dirt or dust. The same is true for sand flies (*Phlebotomus* species). Eight species of *Culicoides* and seven species of *Phlebotomus* have recently been identified in Egypt. The latter is a vector of sandfly fever and leishmaniasis (visceral and cutaneous). Those two zoonoses are unlikely to be confused with either the fifth or sixth plagues.[15]

Unlike the sand fly, which lays it eggs in cracks in walls or stone outcroppings, *Culicoides* larvae feed on abundant microorganisms in decomposing detritus, such as the remains of fish and frogs. The eventual explosive emergence of adult flies might be well construed as a plague coming from "all the dust of the land."

Summary of Interpretations Given to the Ten Plagues of Egypt

Plague *ARAMAIC* *HEBREW*	1. Water to Blood *DAM* דם	2. Swarm of Frogs *TS'FAR-DEI-A* צפרדע	3. Plague of Lice *KI-NIM* כנים	4. Swarms of Flies *A-ROV* ערוב
Biblical Passage	"Stretch out thine hand upon the waters of Egypt: upon their streams, upon their rivers, upon their ponds, upon their pools of water, that they may become blood."	"Stretch forth thine hand with thy rod over the streams, over the rivers, and over the ponds, and cause frogs to come up upon the land of Egypt."	"Aaron stretched out his hand with his rod, and smote the dust of the earth, and it became lice in man, and in the beast; all the dust of the land became lice, through the land of Egypt."	"[T]here came a grievous swarm of flies into the house of the Pharaoh, and into his servants' houses, and into all of the land of Egypt; the land was corrupted by reason of the swarm of flies."
Chapter, Verse	**Exodus 7:19**	**Exodus 8:5**	**Exodus 8:16**	**Exodus 8:24**
Ipuwer Papyrus	"Lo, the river is blood, As one drinks of it one shrinks from the people. And thirsts for water."	"Towns are ravaged, Upper Egypt became wasteland. Lo, crocodiles gorge on their catch."†		
Interpretation				
Bryant England/1810	"tainted and polluted streams"	Frogs (a diety) and their death are emblematic of a prophetic influence	Lice: "vermin . . . pediculi"	(House?) flies representing "Zebub"
Blanc United States/1890	——	Anthrax (*Bacillus anthracis*), infected and killed frogs.	Flies transmitting anthrax	Flies transmitting anthrax
Velikovsky USSR/1950	The fall of red meteorite dust from a comet polluting waters	——	——	——
Hort Netherlands/1957	Red silt, flagellated protozoa *Euglena sanguina, Haematococcus pluvialis*	Anthrax (*Bacillus anthracis*), infected and killed frogs.	Mosquitos (Culex species)	Stable flies (*Stomoxys calcitrans*) transmitting Plagues 5 & 6
Schoental United States/1980	Microfungi and *Fusarium roseum* contaminating waters	Frogs killed by dinoflagellates producing soluble poisons	"vermin"	"flies"
Schmidt Germany/1990	Waters contaminated by dead fish	Frogs	——	Horseflies
Jacoby United States/1990	Nile (a diety) waters made undrinkable secondary to dead fish	Frogs	"Sand fleas," not gnats	"An insect akin to a winged ant"
Hoyte Australia/1993	Dinoflagellates *Gymnodiuium* and *Glenodinium* (unnamed species)	Dehydration and desiccation killed escaping frogs	"Midges" (*Culex antennatus*)	Stable flies *Stomoxys calcitrans* (see Hort)
Ceccarelli Italy/1994	Dinoflagellates *Gymnodiuium* and *Glenodinium* species (after Hoyte)	Frogs	"Midges" *Culex antennatus* (after Hoyte)	Streptococcal and Staphylococcal infections; Babesiosis
Marr, Malloy United States/1996	Freshwater cyanobacteria causing river to turn red, and killing fish	Frogs leave deoxygenated waters and die, contributing to Plague 3	*Culicoides* appear de novo from pupae hatching in sand (Hoyte) transmitting Plague 5	Stable flies (Hort and Hoyte) transmitting Plague 6

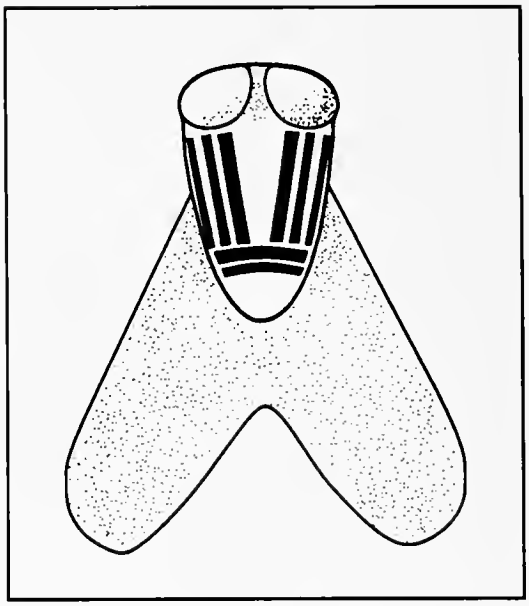
† Some rabbinical scholars have interpreted the Hebraic text as possibly meaning amphibians in general.

5. Animal Murrain *DE-VER* דבר	6. Boils and Blains *SH'HIN* שחין	7. Hailstorms *BA-RAD* ברד	8. Locusts *AR-BEH* ארבה	9. Darkness *HOSHEKH* חשך	10. Death of Eldest *MA-KAT B'KHO-ROT* מכת בכורות
"Behold the hand of the Lord is upon thy cattle which is in the field, upon the horses, upon the asses, upon the camels, upon the oxen, and upon the sheep: there will be a gnevous murrain."	"Take to you handfuls of ashes of the furnace, and let Moses sprinkle it toward the heaven in the sight of the Pharaoh. And it shall become small dust in all the land of Egypt, and shall be a boil breaking forth with blains upon man, and upon beast, throughout all the land of Egypt."	"Stretch forth thine hand toward heaven, that there will be hail in all the land of Egypt, upon man and upon beast, and upon every herb of the field, throughout the land of Egypt."	"[W]hen it was morning, the east wind brought the locusts. And the locusts went up over all the lands of Egypt, and rested in all the coasts of Egypt: very grievous were they; before them there were no such they, neither after them shall be such."	"Moses stretched forth his hand toward heaven; and there was a thick darkness in all the land of Egypt three days: They saw not one another, neither rose from any of his place for three days: but all the Children of Israel had light in their dwellings."	"About midnight I will go out into the midst of Egypt: And all the first-born in the land of Egypt shall die, from the firstborn of Pharaoh that sitteth upon his throne, even unto the firstborn of the maid-servant that is behind the mill; and all the firstborn of the beasts."
Exodus 9:3	**Exodus 9:8**	**Exodus 9:22**	**Exodus 10:13**	**Exodus 10:22**	**Exodus 11:4**
"Lo, all beasts, their hearts shall weep, Cattle bemoan the state of the land."	"Plague is throughout the land. Blood is everywhere."	"Lo, hearts are violent, storms sweep the land."	"Birds find neither fruit nor herbs. . . .Trees are destroyed. No fruit nor herbs are found."	"Lo, the desert claims the land. . . . Those who had shelter are in the dark of the storm. . . Egypt will not be given over [to] sand.. . . The land is not light."	"Ladies suffer like maidservants. . . . Then he who would have smitten the evil, stretched out his arm against it, would have destroyed their seed and their heirs."
"the distemper"	"That where any atom of this dust be whiffed might be entailed, but with a different intention . . a plague and a curse."	"thunder, hail, fire" destroy crops.	Locusts caused famines	"a preternatural state of night"	Confluence of God's will
Anthrax	Anthrax	Hail	Locusts	Locusts swarms	Anthrax
Secondary skin infections from comet dusts	Boils secondary to dusts, blisters from flaming naptha	Dust, gravel, and burning naptha from a comet	———	Cinder dust from a comet	An earthquake
Anthrax	Anthrax	Hailstorms destroyed flax and barley but not wheat or spelt	Locusts	Sandstorms (khamsin)	Famine secondary to destruction of wheat and spelt harvests
Mycotoxins	2° bacteral infect. due to immunosuppression by trichothecenes	Hail	———	———	Mycotoxin-induced death from moldy feeds
———	———	———	Locusts	———	———
———	"herpes-like infection"? "bubonic infection"? "Inflamation of sexual organs"?	Hail	Locusts	Darkness?	———
Surra (debab) (*Trypanasoma evansi*)	Ecthyma (Group A hemoloytic *Streptococcus pyogenes*)	Crops ruined by hailstorms	Locusts ruined crops	Sandstorms	Typhoid fever and salmonelloses (*S. Typhi* and enteriditis)
Babesiosis (*Babesia bigemini*)	Babesiosis (*Babesia bigemini*)	Hail	———	———	———
African horse sickness; Bluetongue; Epizootic hemorrhaghic disease	Glanders (fancy) *Pseudomonas mallei*	Hail destroying established crops and dampening stored foods	Schistocerca gregaria eat all remaining vegetation, including sprouts and seedlings	Sandstorms (khamsin) cover existing food stands and stored food supplies	Mycotoxins specific to stored grains preferentially killed first to access store

Unlike such bloodsucking insects as lice, those tiny, annoying hematophagous flies are not species-specific; they bite both humans and animals with a vengeance, as suggested by one species name, *C. vexans*. Bites can cause severe local reactions, intense itching, and weal formation. Until the late 1960s, *Culicoides* were considered "nuisance" arthropods, incapable of transmitting infectious agents. They are now recognized as biological vectors of a number of human and animal viral diseases. Thus we conclude that *Culicoides* was the cause of the third plague as well as the biological vector for the fifth plague.[16]

The fourth plague, the "swarm of flies," has been given numerous interpretations. Sometimes referred to as "beasts," they should be distinguished from the third plague, although some renditions of the plague account combine those two insects. Hoyte notes that the life cycle and bionomics of the stable fly (*Stomoxys calcitrans, L.*) coincides with the ebbing of the Nile in September, when abundant rotting vegetation fosters ideal harborage for its emerging larvae. Charles Brues listed thirty-one species of Stomoxydinae, including *S. sexvittata Roubaud* (now *S. bilneata Gruenberg*). In addition, *Stomoxys nigra Macquart* occurs throughout Africa and attacks cattle, horses, and people.[17]

Alternative explanations of the "swarm" have been the housefly (*Musca*), tsetse fly (*Glossina*), horsefly (*Tabanus*), and blackfly (*Simulium*). The housefly does not bite. The other three are biters and bloodsuckers, capable of causing severe pain, local irritation, inflammation, and itching. In only two of the fly genera, *Glossina* and *Stomoxys* species, do both the male and female take blood meals. Bites of both flies necessitate ripping of flesh, often leaving open puncture wounds, leading to secondary infections. Unlike the annoying sand fly, the intensity and severity of swarms of both tsetse and stable flies have been reported to induce anemia in penned cattle and stampedes in wild animals. All of the aforementioned flies are capable of transmitting infectious agents (vide infra), but only *Glossina* and *Stomoxys* appear to be appropriate insect vectors for either one or both of the subsequent two plagues. We conclude that the stable fly better fulfills the role as the cause of the fourth plague.



Ancient Egyptian pictograph of a stable fly

(Reproduced with permission from John Baines and Jaromir Malek, Atlas of Ancient Egypt *[New York: Facts on File, 1989])*

The sequelae of the first and second plagues appear to have generated opportunity for plagues three and four. Denied potable water or water in which to bathe, the Egyptians and their livestock would be more exposed to infestation, attack, and secondary infections. Either mechanically or

biologically, at least one kind of fly inoculated pathogenic viral, bacterial, or protozoan organisms into animals and humans, causing subsequent disease. Thus, the third and fourth plagues might be logically linked to the fifth and even the sixth plague.

Fifth and Sixth Plagues—Murrain in Animals and Boils and Blains

The fifth plague is probably the first written record of a true epizootic—a disease inflicted upon animals but not humans. A proper proposal should account for such selectivity, as should the subsequent sixth plague, a zoonosis, which affected both animals and humans. Specifically, the fifth plague struck many hoofed animals—horses, donkeys, camels, cattle (including oxen), and sheep. Hoyte notes that the omission of goats and pigs "is of social, not epidemiologic significance."

Nevertheless, that those animals, which were of common occurrence in Egypt at that time, were not mentioned is relevant, providing negative evidence-clues as to what the plague may have been. The fifth plague, or "murrain," appears to be specific for certain hoofed mammals, sparing domestic pets and wild carnivores, as well as birds, amphibians, and reptiles. In addition to five candidate diseases proposed by previous authors, we propose five other lesser known, arthropod-borne African epizootics infecting hoofed mammals.[18]

Anthrax is a severe bacterial infection capable of being transmitted by various direct and indirect methods, including mechanical transmission by biting flies. Anthrax can infect a wide range of animals, especially goats. Wild animals, including elephants, hippopotami, and impala (but not frogs, as suggested by Hort) can also be infected with anthrax. Those animals, as well as goats and pigs, are not listed or noted in the otherwise complete list of animals affected. Anthrax can also cause human disease; its cutaneous form is associated with a 5–20 percent rate of human mortality, an observation that presumably would have been recorded had it occurred. Anthrax, we believe, is not a viable candidate for the fifth plague.[19]

Rift Valley fever, a viral disease transmitted by various genera of mosquitoes, also can cause illness in humans and may be similarly dismissed. Rift Valley fever causes illness in goats and pigs but spares horses (prominently mentioned as being afflicted). Rinderpest and foot-and-mouth disease are airborne viral infections, but neither affects horses. Two hard tick-borne rickettsial diseases, East Coast fever (*Theiliasis*) and heartwater (*Cowdriosis*) cause illness in cattle but not horses; the former does not cause illness in sheep, and the latter causes disease in goats. Another hard tick-borne disease, babesiosis, is a protozoan disease mimicking malaria and is capable of causing disease in all animals listed. As noted by Hoyte, each equid and ruminant has a different and specific genus of tick vector; moreover, the tick vectors are large, easily recognized during attachment, and likely to have been noted.[20]

Surra, as proposed by Hoyte, is a protozoan disease caused by a trypanosome (*T. brucei evansi*). While responsible for disease limited to equids and ruminants, surra is mechanically transmitted by both tsetse and stable fly bites. Tsetse fly distribution does not extend into northern Egypt, however, and while stable flies are cosmopolitan, the disease's present enzootic range in Africa suggests that it has never penetrated more than 15° north of the equator.

The last two diseases, African horse sickness and bluetongue, are caused by viruses belonging to seventeen different serological

subgroups in the genus *Orbivirus*. Those two RNA viral diseases are biologically transmitted by the same genus, the *Culicoides* midge. African horse sickness is extremely lethal in horses, donkeys, mules and other equines, with a case fatality rate of 95 percent, but it spares other hoofed animals. Bluetongue is variably fatal for cattle, sheep, and goats but not for horses or pigs. Neither disease causes illness in humans, and they are therefore logical choices for the murrain in animals. We therefore propose that those two midge-borne diseases were the cause of the grievous fifth plague among hoofed animals, including goats in the "flock" but not swine. Even though that may be an exception to a unitary explanation, both epizootics best explain the selectivity of animal deaths.[21]

Thus, the earlier plague of lice (*Culicoides* midges) also transmitted two arboviral diseases to hoofed animals. After introduction, disease spread from infected animals to others by many other biting insects, both mechanically and biologically. Over a period of weeks all susceptible animals would have become infected. Only herds and flocks of animals outside the distribution range of *Culicoides* (a notoriously weak flying vector) were spared from those epizootics—i.e., the land of Goshen.

The sixth plague, consisting of boils and blains, struck both humans and "beasts." "Beasts," while not defined, is a true zoonosis that may or may not include some or all domestic and wild animals. Researchers have offered various explanations for that epidemic/epizootic. Blanc's and Hort's proposals of ulcero-glandular anthrax has been alluded to previously as being transmitted by various flies. Hoyte also suggested that stable flies might transmit combined staphylococcal-streptococcal infections—specified as "ecthyma"—to both animals and humans. Giovanni Ceccarelli proposed a variety of strains of babesia as the cause. The latter appears less likely for a number of reasons. The variety of vector-specific ticks that would be needed for multiple-species transmission seems unlikely, and the disease presentations in man and animals have no dermatological symptomatology. Regina Schoental, on the other hand, argues that a transient immunosuppression due to unnamed mycotoxins caused various pathogenic and opportunistic bacterial skin infections as the putative disease and later sequelae.[22]

The disease must have caused severe, suppurative skin infection. Both anthrax and a combined staphylococcal-streptococcal infection fulfill that condition. Both can be transmitted by flies, direct contact, or contaminated food and milk. Spores of anthrax may also be airborne, causing a separate, clinical presentation—mediastinitis. A combined staphylococcal-streptococcal infection is not considered transmitted by the airborne route. A more viable bacterial candidate not previously considered is glanders (*Pseudomonas mallei, farcy*), a highly contagious, airborne zoonotic bacterial disease transmitted by direct contact or through fly bites. First described by Aristotle in 330 B.C.E., glanders is presently found throughout the Middle East and Africa. It is primarily a respiratory infection of horses, donkeys, mules, and goats (cattle are resistant to infection), with lymphatic and metastatic spread to other organs, including the skin or hide. Cutaneous manifestations in equids consist of "cord-like thickening of subcutaneous lymphatics along which are distributed chains of nodules, some of which are ulcerated." Human disease consist of "nodular eruptions on the face, legs,

arms, involvement of the nasal mucosa and later pyemia and metastatic pneumonia."[23]

Whatever the sixth plague—in our opinion, most likely glanders—or the mode by which it was primarily spread—most likely airborne—it may have been further propagated by the ingestion of tainted meat. The major consequence of the plague was further reduction of the protein supply (meat and milk), which had already been dangerously reduced by a fish kill. Again, the Hebrews' animals living in Goshen were spared both the fifth plague (African horse sickness and bluetongue) and sixth plague (glanders).

The Seventh and Eighth Plagues—Hail and Locusts

Hail occurs throughout the temperate and tropical worlds, usually seasonally. Caused by collisions of supercooled water in cumulonimbus clouds, hailstones may have a diameter of 2mm to 13cm (1/16th inch to five inches). Larger hailstones have killed unprotected humans and animals; smaller stones can still cause severe damage and destruction to smaller animals and to crops. The hail described in the biblical account would have been certainly severe enough to kill or maim both humans and animals caught in the fields. More important, the hailstorms would have devastated the seasonal fruit, vegetable, and grain crops of the Egyptians at a time when they depended on their yield to last through the following year. That was the antepenultimate assault on the Egyptians' existing food supply, which would be further tested by the eighth plague, whence Egyptians would have to rely on their meager reserves.

The desert locust (*Schistocerca gregaria*) is specific to Africa, the Middle East, and India; it may occur in swarms and persist in a region for as long as several years. That those insects were known and revered, if not feared, is recorded on ancient Egyptian friezes predating the plagues. Transformed from solitary grasshoppers by as-yet-unexplained factors (presumably food-dependent), locusts swarm and become "gregarious," attacking all known standing crops. They consume all plant crops and seedlings, acting to cleanse an area of all living vegetation, whether food or not. The locust swarms, coming soon after the plague of hail—which would have damaged fruit-trees and vegetable crops—would have precipitated great urgency on the part of the Egyptians to save their fallen, wilting stands. Partially damaged crops would have been hastily carried to protected sheltered granaries and underground storage facilities. The crops would have been broken and dampened by hail, damaged by immersion in fields, and contaminated by insect feces (rich in bacterial and fungal microorganisms).[24]

The Ninth and Tenth Plagues—Darkness and Death of the Eldest

However darkness reigned over Egypt for three days and nights, it prevented Egyptians from leaving their homes or even moving within their homes. The Hebrews in Goshen were not affected by the ninth plague. Hort acknowledges Georg Ebers's proposal that a volcanic eruption may have accounted for the phenomenon, but she noted no corroborative evidence. The same might be said for Velikovsky's theory of "gravel" from a passing comet. Hort's proposal that the darkness was due to a *khamsin*, a hot southerly wind coming from the Sahara, is most convincing. She suggests that the fierce, hot winds would have picked up ultrasmall particles of sand, creating a sandstorm so

massive that it nearly eclipsed the sun in a dark yellow haze. She notes that the particular *khamsin* causing the sandstorm would have to be the first of many experienced in Egypt during *khamsin* season (March through May), which is in keeping with her timetable that the ninth plague must have occurred in March. The first of those seasonal windstorms would be the worst, picking up all accumulated fine sand from the previous year; once deposited on land, the sand would cause massive drifts and dunes of ultrafine sand in the lees of houses, making entrance and egress impossible. Severe storms (*sobaa*) commonly last for two or three days, covering small houses and shelters. Years and decades of seasonal *khamsins* cause the disappearance of ancient monuments, tombs, and cities that archaeologists are continuing to discover in the upper Nile region of Egypt.[25]

Hort is strangely cursory in her explanation of the tenth plague, offering little in the form of exegesis. She considered the plague an extension of the previous nine plagues in bringing the Egyptian Empire closer to starvation. A novel interpretation offered is that "first-born" may have been an inadvertent translation of the Hebraic first-born בכר for first-fruits בכר׳ם . She suggested that the Hebrew people, who had normal stores of "corn," anticipated a conflict with Egyptians. The Egyptians were bereft of food (fish and meat), crops (wheat, barley, emmer, spelt, fruit), and even the ability to till soil (due to the death of the beast of burden). They could not expect new crops due to the destruction of crops and new seedlings by the preceding hailstorms and locusts. The ninth plague—a sandstorm—covered the remaining tillable land.[26]

Alternative explanations also build on the accumulative disruptions either exclusively inflicted upon only Egyptians—the fourth, fifth, sixth, seventh, and ninth plagues—or Egypt as a whole (including Goshen), the first, second, third, and eighth plague. Specific diseases (e.g., anthraxm or typhoid), or catastrophes (e.g., an earthquake) may, in part, explain preferential deaths of Egyptians since Goshen was geographically separate and spared from those occurrences. Those explanations are nevertheless limited. First, the symptoms of anthrax—cutaneous or pulmonic—are fairly dramatic, as is the destruction brought on by an earthquake. If the account of the Ten Plagues included boils and blains and a hailstorm, one would argue that a description of the symptoms and events around the tenth plague would also have been offered. Neither an anthrax epidemic nor an earthquake are in concert with previous plagues, building as they did on a theme of an impending famine caused by a decreasing supply of food.[27]

Hort's suggestion that death of the first-fruits (i.e., sprouts) may have been, more than figuratively, the final insult. The cataclysmic consequences of the last and most serious plague (the death of an estimated 10 percent of all humans and animals) is not studiously considered by Hort. Hoyte, by contrast, in considering the sequelae of a compromised food supply, offers an explanation of a form of food poisoning from contaminated foodstuffs (consumed by humans and animals) as a possible cause. The specific infections causing the epidemic and zoonosis proposed by Hoyte are, respectively, typhoid fever (*Salmonella typhi*) and salmonellosis (*Salmonella typhimurium*). Those two infections are posited because the former does not cause illness in animals and the latter causes infection in both man and animals. They have different incubation periods (weeks for typhoid, days for salmonellosis).

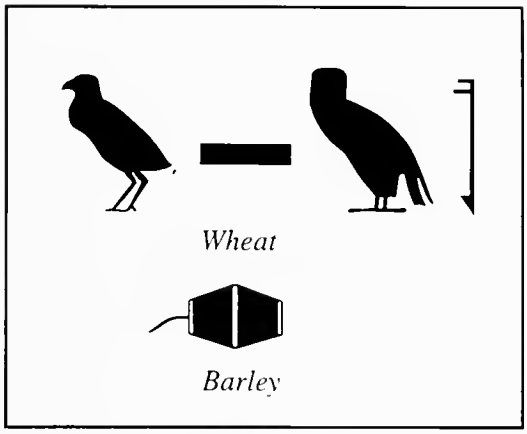
Both infections have different gastrointestinal and extragastrointestinal presentations. Both may cause death, but only after many days or weeks of illness—not immediately.[28]

Possible clues to the cause of the tenth plague include (1) its unitary nature, (2) the very *lack* of a description given to it, and (3) its sudden nature. Aside from an immediate, overnight death of large numbers of eldest-born humans and animals throughout Egypt, no symptoms are recorded. As with anthrax, typhoid, salmonellosis, babesiosis, and an earthquake, an infectious disease or natural calamity usually has physical manifestations that might be expected to be noted and recorded. Only if man and beast were to be suddenly, and quite literally, dropped in their tracks, within minutes or hours after exposure, would one expect no description of prodromata, symptoms, or a prolonged clinical course. If such a single cause is offered and is in keeping with that premise, it should also take into consideration the influence of the previous nine plagues. Finally, it should explain the preferential death of the eldest human and animal.

Hypothesis for the Cause of the Tenth Plague

Such an explanation for the tenth plague does exist, but its very existence was not known until a few years ago. What follows is a review of the preceding plagues and their consequences:

- The freshwater supplies of the upper Nile Delta were made undrinkable and, months later, suspect.
- Fish, an important supply of protein, were lost for a time; they, like the water, were considered a suspect source of food.
- Frogs died, allowing insects to multiply unheeded.



Egyptian hieroglyphics

(Reproduced with permission from William J. Darby, Paul Ghalioungui, and Louis Grivetti, Food: The Gift of Osiris *[New York: Academic Press, 1977])*

- Animal protein from cattle, sheep, goats, and swine were demonstrably tainted or reduced through illnesses.
- Such draft animals as horses, donkeys, and oxen were afflicted, and harvests were thus left largely unattended.
- Field crops were destroyed by hail and water, left to rot, or picked hastily.
- Locusts consumed the remaining vegetation, particularly young shoots that might have offered the hope of new crops.
- A sandstorm covered all obvious remaining sources of food supplies, and provided a blanket of warmth, humidity, and darkness for water-soaked foodstuffs buried beneath the sand to rot.
- The 2.5 million people of the Egyptian nation were starving after ten months of ill fortune.
- A mysterious affliction then killed the eldest Egyptian and the eldest of animals in a sudden strike, without any explanation other than Yahweh's will.

Would any known natural phenomenon explain the above? Noteworthy is Schoental, who first suggested that mycotoxins in contaminating stored foodstuffs could explain

the sudden death of Egyptian males and animals. In a brief paragraph from a larger exposition, "Mycotoxins in the Bible," she suggested that the most dominant humans and animals probably had the earliest access to the stored, moldy food supplies, which of course were fatal. The nature of those food supplies, the specific mycotoxin(s) infecting them, the specific cause(s) of death, and the logical explanation of a lack of symptoms for those deaths could not be addressed, however, as the causative agents had yet to be identified.[29]

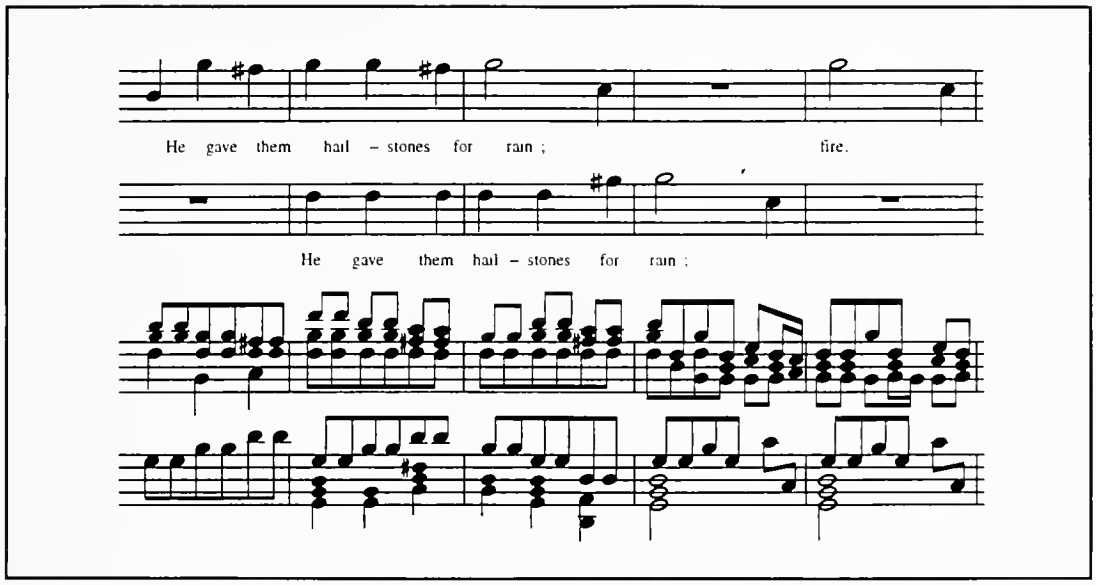
Very much like species-specific arthropod vectors and host-specific disease agents, mycotoxin-producing fungi are also plant-specific in foodstuffs they attack. Toxins produced by those fungi also vary in mutagenic, carcinogenic, and toxicologic properties. By analyzing foodstuffs available to Egyptians (and their animals) at the time of the Exodus, one may be able to identify likely candidate mycotoxins that may have caused sudden illness in both humans and livestock.[30]

Egyptian foods and food reserves have been well documented. Indeed, William J. Darby and his colleagues state that the second most important and powerful position in the Egyptian government was keeper of the granaries because periodic famine had instilled careful planning on the part of the pharaohs. Most crucial of all foodstuffs were the grains, specifically barley and wheat. The early precursors of what today is called "wheat" were, during the second millennium B.C.E., the precursor grains, spelt and emmer. Other grains in evidence at that time were sorghum, rye, and "corn."[31]

During the time of Thutmose III, barley was largely used to make a primitive beer. Spelt and emmer was used to make bread, and stored as a commodity for future need or trade. Sorghum was either limited in use or used for trade. Rye was not yet introduced. "Corn," as translated by the Scriptures, must have been any early form of wheat since true "corn" (maize), as we know it, is a New World vegetable. The talmudic and biblical terms "corn" must, by force, signify a wheatlike product, perhaps emmer or spelt. A distinction among those grains is important, since it allows a differential analysis to be made regarding mycotoxins.

More than one hundred toxigenic fungi have been identified since the first mycotoxin, aflatoxin, was discovered in 1961. Dozens have been identified as causing natural outbreaks in human and animal populations; only a few, however, have been traced to standing or stored grains of economic importance used for food and fodder. The specific genera of those fungi are *Claviceps, Aspergillus, Penicillium, Fusarium,* and a variety of lesser organisms. The most potent mycotoxins within those four genera that are specific for wheat are the stachybotryotoxicoses produced by Fusarium *graminearum* and *Stachybotrys atra*. The mycotoxins produced (macrocyclic trichothecenes) have been linked to the deaths of thousands of people and animals in the former USSR during World War II, as well as a variety of livestock (poultry, cattle, horses, sheep, and swine) in many countries. Humans ingest products from grain, such as bread; poultry eat grain, equids consume fodder, and ruminants (cows, oxen, and camels) eat straw. (Of interest, ruminant animals are preferentially attracted to damp straw on which *S. atra* grows.)[32]

More recently, *S. atra* mycotoxins caused illness and deaths in humans who have had no direct contact with mycotoxins other than inhaling them. Trichothecene mycotoxins produced on walls and basement floors in



Handel's interpretation of the plague of hail, in Israel in Egypt

water-damaged buildings were carried to their victims through ventilation systems. A similar exposure in a farming couple caused bronchiolitis in the man and acute renal failure in the woman, both of whom had been working in a silo and were exposed to *Aspergillus ochraceus*. Mycotoxins have also been hypothesized as an explanation for illness and death among archaeologists, made famous in the so-called "King Tut's curse."[33] (The Earl of Carnarvon, discoverer of King Tut'ankhamun's tomb, died of unexplained pneumonia in 1922.)

Although macrocyclic trichothecenes vary in toxicity and cytotoxicity in laboratory animals, it is apparent that very small amounts cause illness and death. Fusty, *di minimis* amounts of *S. atra*-induced mycotoxicosis are now being recognized as a possible cause of "sick-building syndrome." Chronic low exposures can cause (as originally suggested by Schoental) granulocytopenia and increased susceptibility to bacterial infection. Acute, large exposures cause immediate symptoms of gastrointestinal irritation, petechial hemorrhage, and massive internal bleeding, resulting in sudden death.[34]

Conclusion

The sudden death of Egyptian people and their animals may be due to the precipitous raid of improperly stored grains, fodder, and foodstuffs. Elder, more responsible, or more powerful individuals would have had first access to granaries and may have inhaled aerosolized *S. atra* mycotoxins. Those people would also be first to eat the breads or drink the beer produced from the moldy wheat and barley, respectively. Similarly, the more dominant animals would eat grain and straw on which a patina of mycotoxin-producing fungi grew. Soon thereafter, acute symptoms and sudden deaths may have alerted both man and animal of the danger in ingesting the grains and grain

products. Subsequently, once granaries had been aired, the inhalational route was no longer a factor. In addition, deeper stores of wheat and barley may have not been as heavily contaminated by the surface-growing fungi, and therefore, relatively safer to eat—sparing less powerful man and beast. The Hebrews in Goshen, who had experienced neither the calumny of tainted fish and meat nor the destruction of crops, nor famine, would also have avoided the mass-poisoning due to those mycotoxins.

That, then, is our explanation for the most devastating, tenth and last plague of Egypt, and the proceeding plagues that may have contributed to it. Numerous theologians and biblical scholars have authored previous, significant, original, and unique contributions to the eclectic interpretation of causes of the Ten Plagues (most notably Hort, Hoyte, and Schoental). We greatly acknowledge their hypotheses and add our interpretation and a final synthesis to that impressive collection of literature. It is a tragic and powerful story of two proud peoples—the Egyptians, under Thutmose III at the height of their empire, and the people of Israel about to become a nation. We hope that others might wish to begin where we concluded, and to follow with their own interpretations.

We end with this note: The long Jewish tradition about the first Passover began at the end of the ninth plague. It is a celebration of the first meal to mark the Hebrews' escape from the many plagues, and from the tenth plague. The Passover celebration consists of eating symbolic newborn, healthy lamb shank, fresh herbs, and horseradish—all safe from mycotoxin exposure. It also requires eating unleavened bread made from fresh flour, which is, by definition, free of any yeasty or other mycotoxin contamination.

♦

Notes

1. Curtis. D. Malloy et al., "Emerging Pathogens: The White Horse of the Apocalypse?" *Journal of Public Health Management and Practice* 1 (1995): 48–61; Mary E. Wilson, Richard Levins, and Andrew Spielman, eds., *Disease in Evolution: Global Changes and Emergence of Infectious Diseases*, vol. 740, Annals of the New York Academy of Sciences (New York: Academy of Sciences, 1994), 1–503.

2. All references are to the Authorized (King James) Version.

3. Immanuel Velikovsky, *Worlds in Collision* (Garden City, N.Y.: Doubleday, 1950), 49; Velikovsky, *Ages in Chaos* (London: Sphere Books, 1973), 41–44; "The Admonitions of Ipuwer, Papyrus Leiden 344, Recto," in *Ancient Egyptian Literature: A Book of Readings*, ed. Miriam Lichtheim, 3 vols. (Berkeley: University of California Press, 1973), 1:149–63.

4. Greta Hort, "The Plagues of Egypt," *Zeitschrift fur die Altesttamentliche Wissenschaft* 69 (1957): 84–103; Hort, "The Plagues of Egypt," *Zeitschrift fur die Altesttamentliche Wissenschaft* 70 (1958): 48–59.

5. Donovan A. Courville, *The Exodus Problem and Its Ramifications* (Loma Linda, Calif.: Challenge Books, 1978), 116–32; *The Ten Commandments*, Paramount Pictures, Hollywood, Calif., 1956; Werner Keller, *The Bible as History* (New York: William Morrow and Co., 1981), 122; H. M. D. Hoyte, "The Plagues of Egypt: What Killed the Animals and Firstborn?" *Medical Journal of Australia* 158 (1993): 706–8; John J. Bimson, *Redating the Exodus and the Conquest* (Sheffield, Eng.: Almond Press, 1981); John Baines and Jaromir Malek, *Atlas of Ancient Egypt* (New York: Facts on File, 1989), 36.

6. Baines and Malek, *Atlas*, 36.

7. Martin Gilbert, *Jewish History Atlas* (London: Weidenfeld and Nicolson, 1976), 312; Courville, *Exodus Problem*, 116–32.

8. It is interesting that Isaac Asimov, in his comprehensive *Asimov's History of the Bible: The Old Testament*, provided no interpretation regarding the Ten Plagues. See *Asimov's History of the Bible: The Old Testament* (New York: Doubleday, 1968), 1–1295.

9. Jacob Bryant, *Observations upon the Plagues Inflicted upon the Egyptians* (London: Hamilton and H. Ogle, 1810), 1–392. Velikovsky's book and his theories cannot be expanded upon here. However, it must be noted that his hypothesis about a comet and its subsequent damage, ostensibly incredulous when he wrote his book in 1950, may be partially substantiated by "Bits of Mars Hit Africa in '62, Researchers Say," *New York Times*, March 31, 1995, A16, which suggests that an explosion on Mars millions of years ago produced material that landed on Earth at least three times, the most recent of which was in Nigeria. Furthermore, Velikovsky's belief that a volcanic eruption might have served as one of many cataclysmic catastrophes causing the plagues of Egypt is supported by a 1783 volcanic eruption described in Stuart Flexner with Doris Flexner, *The Pessimist's Guide to History* (New York: Avon Books, 1992), 95.

10. P. A. Tester, "Harmful Marine Phytoplankton and Shellfish Toxicity: Potential Consequences of Climate Change," in *Disease in Evolution*, 69–76; E. C. D. Todd, "Emerging Diseases Associated with Seafood Toxins and Other Water-Borne Agents," in *Disease in Evolution*, 77–94; Wayne W. Carmichael and Ian R. Falconer, "Diseases Related to Freshwater Blue-Green Algal Toxins and Control Measures," *Algal Toxins in Seafood and Drinking Water*, ed. Falconer (London: Academic Press, Ltd., 1993), 188–209; JoAnn M. Burkholder, H. B. Glasgow, and Karen A. Steidinger, "Unravelling Environmental and Trophic Controls on Stage Transformations in the Complex Life Cycle of an Ichthyotoxic 'Ambush Predator' Dinoflagellate," abstract from the Sixth International Conference on Toxic Marine Phytoplankton, Nantes, France, Oct. 18–22, 1993.

11. William J. Darby, Paul Ghalioungui, and Louis Grivetti, *Food: The Gift of Osiris*, 2 vols. (New York: Academic Press, 1977), 1:337.

12. Personal communication from Richard L. Brown, Ph.D., Curator, Mississippi Entomological Museum, Mississippi State University, July 24, 1995; Defense Pest Management Information Center, *Disease Vector Ecology Profile: Egypt*, Technical Information Bulletin (Washington, D.C.: Forest Glen Section, Walter Reed Army Medical Center, 1988), 1–48.

13. Personal communication from David J. Sencer, M.D., M.P.H., Centers for Disease Control (retired), July 27, 1995.

14. Hoyte, "Plagues of Egypt," 706–8.

15. *Disease Vector Ecology Profile*.

16. Maurice T. James and Robert F. Harwood, *Herms's Medical Entomology*, 6th ed. (New York: Macmillan and Company, 1969), 161–64.

17. Hoyte, "Plagues of Egypt"; Charles T. Brues, "Geographic Distribution of the Stable Fly, *Stomoxys calcitrans*," *Journal of Economic Entomology* 6 (1913): 459–77; Brown communication.

18. Hoyte, "Plagues of Egypt," 706–8.

19. Abram S. Benenson, ed., *Control of Communicable Disease in Man* (Washington, D.C.: American Public Health Association, 1990), 17.

20. Committee on Foreign Animal Diseases, *Foreign Animal Diseases* (Richmond, Va.: United States Animal Health Association, 1992), 1–424; Benenson, *Control of Communicable Disease*, 54; Paul F. Cranefield, *Science and Empire: East Coast Fever in Rhodesia and the Transvaal* (Cambridge, Eng.: Cambridge University Press, 1991), 1–385.

21. Committee on Foreign Animal Diseases, *Foreign Animal Diseases*. According to Rabbi Nosson Scherman, the fifth plague could not have killed all the animals of Egypt (as verse 6 states) but only the animals in the field. Spared were all animals in Goshen, sheltered Egyptian ruminants and equids, and domestic household pets. That interpretation facilitates the explanation of the next epidemic, when both humans and surviving "beasts" were afflicted. It also allows for a solution to the question of where the pharaoh obtained the horses necessary to pursue the Hebrews during the subsequent Exodus. Scherman, *The Chumash: The Torah: Haftaros and Five Megillos with a Commentary Anthologized from the Rabbinic Writings*, ArtScroll series (Brooklyn: Mesorah Publications, Ltd., 1993), 1–313.

22. Hort, "Plagues of Egypt," 69: 84–103, and 70: 48–59; Henry W. Blanc, *Anthrax: The Disease of the Egyptian Plagues*, rpt. from *New Orleans Medical and Surgical Journal*, July 1890; G. Ceccarelli, "Le dieci piaghe d'Egitto e la loro interpretazione medica," *Minerva Medica* 85, no. 5 (1994): 271–77; Regina Schoental, "A Corner of History: Moses and Mycotoxins," *Preventive Medicine* 9 (1980): 159–61; Schoental, "Mycotoxins and the Bible," *Perspectives in Biology and Medicine* 28 (Autumn 1984): 117–20.

23. Committee on Foreign Animal Diseases, Foreign Animal Diseases.

24. Robert A. Cheke and Johnson Holt, "Complex Dynamics of Desert Locust Plagues," *Ecological Entomology* 18 (1993): 109–15; Darby et al., *Food*, 1:337.

25. Hort, "Plagues of Egypt," 70: 48–59; Velikovsky, *Worlds in Collision*; personal communication from W. Benson Harer, Jr., physician and Egyptologist, July 20, 1995.

26. Hort, "Plagues of Egypt," 70: 48–59.

27. Velikovsky, *Worlds in Collision*; Velikovsky, *Ages in Chaos*; Hort, "Plagues of Egypt," 69: 84–103 and 70: 48–59; Benenson, *Control of Communicable Disease*, 17; Schoental, "Corner of History," 159–61; Ludwig Schmidt, *Beobachtungen zu der plagenerzählung in Exodus VII 14–XI 10* (Leiden: E. J. Brill, 1990), 1–23; M. G. Jacoby, "The Fifth Plague of Egypt," *Journal of the American Medical Association* 249 (1983): 2779–80.

28. Hoyte, "Plagues of Egypt," 706–8; Benenson, *Control of Communicable Disease*, 469, 381.

29. Schoental, "Corner of History," 159–61; Schoental, "Mycotoxins," 117–20.

30. Raghubir P. Sharma and Dattajirao K. Salunkhe, *Mycotoxins and Phytoalexins* (Boca Raton, Fla.: CRC Press, 1991), 68–73.

31. Darby et al., *Food*, 457–99.

32. Sharma and Salunkhe, *Mycotoxins*, 68–73; D. Carleton Gajdusek, *Alimentary Toxic Aleukia in Acute Infectious Hemorrhagic Fevers and Mycotoxins in the Union of Soviet Socialist Republics*, Medical Science Publication, no. 2 (Washington, D.C.: Army Medical

Service Graduate School, Walter Reed Army Medical Center, 1953), 34.

33. W. A. Croft, "Airborne Outbreak of Tricothecene Toxicosis," *Atmospheric Environment* 20 (1986): 542–52; personal communication from Eduardo Montaña, M.D., Centers for Disease Control and Prevention, Atlanta, June 25, 1995; N. DiPaulo et al., "Inhaled Mycotoxins Lead to Acute Renal Failure," *Nephrology Dialysis Transplantation* 9, suppl. 4 (1994): 116–20.

34. Sharma and Salunkhe, *Mycotoxins*, 1–775; Eckardt Johanning, "Health Problems Related to Fungal Exposure: The Example of Toxigenic Stachybotrys Chartrum Atra," *Fungi and Bacteria in Indoor Air Environments*, ed. Johanning and C. S. Yang (New York: Eastern New York Occupational Health Program, 1995), 169–82.

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Cholera: Outlook for the Twenty-First Century

John P. Craig

Cholera is at once the best understood of infectious diseases and also the most unpredictable in its appearance in time and place. Treatment is among the most successful in all of medicine, yet prevention is difficult to achieve. An approximation of the sketchy history of cholera epidemics and pandemics of the nineteenth and twentieth centuries as recorded by Western observers is shown in Figure 1.

Asiatic cholera was first recognized by Western medicine in the second decade of the nineteenth century, and medical historians have recorded seven pandemics since then. A quick scan of Figure 1 might suggest to the skeptical observer that the division of the human cholera experience into seven pandemics has been quite arbitrary because it shows pretty clearly that since 1817 we have been in the throes of cholera epidemics more often than not. What is most fascinating and still unexplained is that there have been occasional periods during which cholera seemed to vanish from all parts of the Western world—at least to undetectable levels—and then resurfaced in unanticipated regions. No other infectious disease capable of causing such high rates of morbidity and mortality has exhibited that manner of recurrent epidemic explosiveness following near-total disappearance from all parts of the world except for its permanent annual presence in the Gangetic delta of the Indian subcontinent.

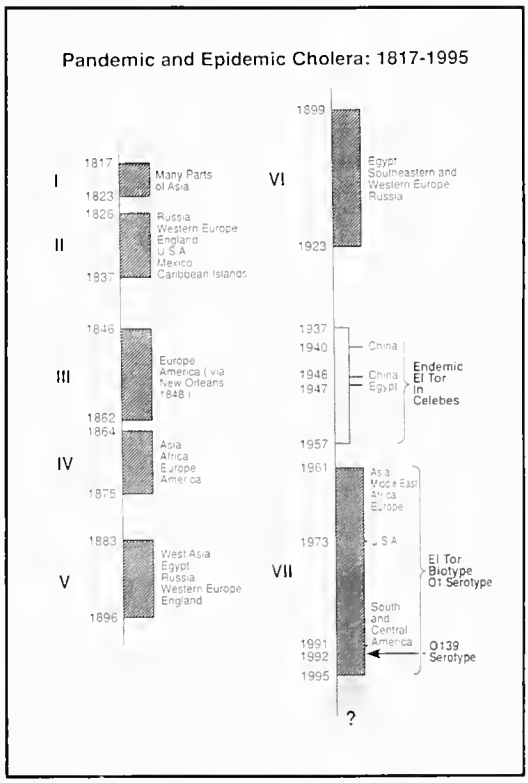

Fig. 1. Years and regions of the Seven Cholera Pandemics.

Three Steps Forward

During the era shown in Figure 1, lasting more than a century and a half, there have been three major bursts of enlightenment concerning the disease. The first recognized its contagious nature; the second revealed

the microbial agent responsible; and the third, coincident with the current Seventh Pandemic, has disclosed the essential mechanisms of pathogenesis and has prescribed an astonishingly effective therapy. Unlike several other human scourges in which pathogenesis and treatment have been elucidated much less successfully, however, cholera has defied our attempts to develop a truly effective and applicable immunizing agent. It still eludes our efforts to understand the factors that determine its periodic emergence in epidemic form. Cholera stands in striking contrast to smallpox, in which the most eminently successful of all vaccines was perfected, applied, and led to the eradication of the disease before the mechanisms of pathogenesis were fully understood (and before any treatment of significance had been devised).

All three bursts of enlightenment in cholera followed on the heels of a new pandemic that provided investigators with an abundance of patients and the opportunity to study them.

The first was John Snow's recognition of the contagious nature of the disease and its dependence on drinking water for entry into the human host.[1] Snow postulated during the 1854 cholera epidemic in London that a materia morbis capable of replicating in the human host was transferred from one patient to the next in the diluted liquid discharges that found their way into the water distribution system. Snow also proposed that once the entity had reached the bowel of the next victim it multiplied and produced a poison that caused the bowel to secrete its normal intestinal juice in prodigious quantities, thus leading to the well-known voluminous secretory diarrhea and hypovolemic shock that characterizes the severe form of the disease. Snow's series of observations and his brilliant and simple exposition of his findings represented a fundamental leap into a new dimension of understanding of infectious disease, decades before the microbial era. A careful reading of his scholarly treatise will disclose an astonishing prescience in his descriptions and in his interpretations of his findings.

The second burst of understanding came with Robert Koch's discovery in Egypt during the Fifth Pandemic that a bacillus, which he dubbed *Vibrio comma*, is the probable microbial agent of the disease.[2] Koch was unable to fulfill the third of his own postulates—which he proposed as the prerequisites for proof of causality of any disease.[3] Nevertheless, he laid the foundation for the spate of research that followed eighty years later when the Seventh Pandemic rekindled the curiosity of the medical world and led to a clearer understanding of the manner by which Snow's materia morbis could wreak such sudden havoc on its victims. It was left to Richard B. Hornick and his associates at the University of Maryland to fulfill the third of Koch's postulates with landmark studies that reproduced typical clinical cholera in volunteers in 1971.[4]

The third burst of understanding about the nature of cholera was stimulated by the current Seventh Pandemic, which began in 1961. Thus, since the 1960s—and continuing today—there has been a steady outpouring of research that has led to a detailed understanding of the structure of Koch's kommabacillus (now renamed *Vibrio cholerae*) and of its many products—most notably the cholera enterotoxin, an excreted protein that appears to be the chief but probably not the sole entity responsible for the hypersecretion of succus entericus that Snow so eloquently described more than a century earlier.[5]

Although scientific literature now abounds with studies dealing with the mechanisms of pathogenesis of cholera, it is my opinion that the seminal work that fired the imaginations of all who followed was that of Sambhu Nath De of Calcutta.[6] De showed in 1958, just before the beginning of the current pandemic, that the cholera vibrio produces an enterotoxin that is responsible for the dramatic fluid and electrolyte losses that make the disease so feared and respected. It is also abundantly clear that the major biomedical triumph emerging from the laboratory and clinical research stimulated by the massive morbidity of the Seventh Pandemic has been the near-perfection of the treatment of patients with cholera. It is an unparalleled victory in the annals of medicine and is the result of years of painstaking clinical investigation by scores of physicians from many countries. Today, in the hands of well-trained physicians (and, even more notably, paramedical personnel), there can be a 99 percent survival of patients with even the most severe form of the disease with the proper use of intravenous and oral fluid and electrolyte replacement therapy. In no other disease in which untreated patients suffer such high fatality rates can such dramatically successful results be even hoped for. That fact was triumphantly demonstrated in the present ongoing epidemic in South and Central America (vida infra), in which local physicians and other health care deliverers achieved just such near-miraculous salvation of life with less than one percent case-fatality rates.

Cholera is thus unique in that at present the protection of human life depends upon treatment of the disease after onset rather than prevention by vaccination or interruption of transmission. The latter may appear ironic upon first thought; unlike an airborne infection we clearly know how to disinfect an individual's intake of food or drink, but because of our ignorance of the ecology of vibrios in the environment, that theoretical knowledge cannot yet be translated into realistic protection of most of the communities or societies of our world. An approach that differs fundamentally from the control of smallpox or tuberculosis will be required to prevent cholera from recurring indefinitely into the future, often in epidemic proportions, in all but the minority of well-sanitated societies of the world.

By 1991, the Seventh Pandemic had persisted longer by many years than any of the earlier six. Having begun in 1961, it was well into its thirtieth year. It had spread along most of the major trade and travel routes in the footsteps of the previous epidemics across Asia, the Middle East, and into southern Europe. In 1970 it re-seeded sub-Saharan Africa for the first time in this century; within two years, more than thirty central African countries had suffered significant—and, in many cases, major—epidemics with case-fatality rates of 6 percent to 30 percent.[7] It now appears that cholera has become endemic for the foreseeable future in central Africa. Increased urbanization and an inability to provide enough clean water for the burgeoning populations have prevented health officials from breaking the chain of human-to-human spread.

In 1973 cholera appeared along the United States Gulf Coast, but only as widely scattered isolated cases and clusters that did not lead to human-to-human spread. That strain of the cholera vibrio was later demonstrated to be quite distinct from the Eurasian and African strain, suggesting that, although temporally associated with the Seventh Pandemic, it arose independently from a nonhuman environmental source.[8] It failed to

spread because the rural communities in which it occurred (Texas, Louisiana, and Florida) enjoyed better arrangements for the disposal of human feces than did most of the earlier diseased areas of Asia and Africa.

The late 1970s and the 1980s did not witness a significant spread of cholera to new areas of the globe. Medical and public health communities had become rather accustomed to the notion that cholera would remain endemic in those communities in the Old World where the chain of contagion could not be fully broken as long as public sanitation suffered from an unsurmountable level of stagnation. Everyone knew how cholera spread, and everyone knew what needed to be done to eradicate epidemic disease (if not sporadic self-limited outbreaks). Nevertheless, the ability to translate that know-how into a universal clean water and clean food distribution system was beyond the reach of the majority of communities in the developing nations.

During the same period, many observers noted that much of Central America and South America suffered from a lack of public and private sanitation that seemed to invite the invasion of cholera into both rural and urban areas. Although most large cities had long ago installed water distribution, filtration, and chlorination systems that should have provided an effective barrier to the wholesale spread of cholera, many segments of the rapidly growing urban areas did not enjoy the benefits of individual household water and sanitation facilities. Some systems failed to provide adequate chlorination to prevent the distribution of pathogens to individual households. Protection of food preparation from contamination by infected food handlers was often inadequate. Yet, for thirty years since the beginning of the Seventh Pandemic, no confirmed cases of cholera were reported from any of the countries of Central America or South America.

It was clear that that region of the world did not enjoy a natural barrier to the survival and spread of cholera, since there had been well-documented epidemics in the nineteenth century when the earlier pandemics spread throughout the world.[9] Transportation by both sea and air had expanded tremendously during the twentieth century, affording numerous opportunities for the introduction of cholera from Asia, Europe, or Africa during the decades in which those continents were being thoroughly seeded with the El Tor strain of *Vibrio cholerae*. Nontoxinogenic and hence nonpathogenic strains of the organism were repeatedly isolated from surface waters and sewers in Brazil and, if they had been looked for, could probably have been found in many other countries of the continent. No substantiated reason exists for supposing that ecological requirements for the survival and propagation of fully pathogenic strains of the organism differ significantly from those of nonpathogenic strains. The endemic pathogenic North American strain was no doubt continually present in northern coastal waters of the Gulf of Mexico. Yet, as measured by historic fact, no effective introduction of pathogenic cholera vibrios into South America or Central America took place until 1991.

The Latin Invasion

In the last week of January 1991, doctors and public health officials of Peru were jolted by the sudden appearance of explosive outbreaks of cholera in three coastal cities.[10] The first outbreak was in the city of Chancay, sixty kilometers north of Lima. On the very next day an outbreak was reported from Chimbote, a seaport four hundred kilo-

meters north of Chancay. Cases in both cities were bacteriologically confirmed on January 31. The outbreak spread rapidly, and by the seventh of February there were confirmed cases in at least four areas along the Peruvian coast from the Chilean to the Ecuadorian border—a distance of more than two thousand kilometers. It seemed then, and still seems, unlikely that contiguous spread along land routes, even by travellers, could have explained the virtually simultaneous appearance of cholera over such a wide expanse of shoreline. By February 12, epidemics were reported from communities fifty to 150 kilometers inland, and by February 20 there were reported cases from the Andean highlands. In attempting to explain the explosive dispersal of the infecting organisms that necessarily preceded the onset of disease, at least two mechanisms can, in theory, be considered.

The only mechanism that was publicly considered to have been operative was the postulated new introduction of very large numbers of pathogenic vibrios into Peruvian coastal waters by the only source known capable of such delivery—namely, ships carrying contaminated bilge. Pan American Health Organization officials have postulated that the bacteria first arrived with a Chinese freighter, which is presumed to have released its bilge water into the harbor at Lima. If that was a one-time introduction, how does one account for the fact that the first recognized cases were in Chancay, sixty kilometers north of Lima, and one day later in Chimbote, a seaport four hundred kilometers north of Chancay? Favorable climatological conditions could theoretically have allowed amplification at sea—either in open water, or following colonization of phyto- or zooplankton—leading to massive contamination of seafood that was eaten by residents of the coastal cities. Those patients could have subsequently contaminated the inadequately chlorinated water supply of each city, leading to a further amplification of transmission by the second route. Inland spread would have to be explained by the consumption of contaminated seafood brought to the interior by surface vehicles. Feces from the first generation of patients would then have had to contaminate the local water supplies. In any scenario, heavy contamination of many separate water supply systems accompanied by totally inadequate decontamination before distribution would be required to account for the high morbidity that took place in Peru and surrounding countries.

Indeed, it has now been reported that during the 1980s many local Peruvian water officials decided to discontinue the chlorination of urban wells that served as sources for municipal water distribution systems.[11] After the epidemic began, some local water officials cited United States Environmental Protection Agency studies showing that chlorine may create a slight cancer risk as justification for discontinuation of routine chlorination of their water supplies. It seems to have been a case of risk assessment gone wrong!

A second possible immediate source of the pathogenic vibrios is one that does not seem to have been given serious public consideration—a sudden and massive expansion of a preexisting small population of pathogenic cholera vibrios on zoo- or phytoplankton in Peruvian coastal waters. No matter how remote the possibility seems on first consideration, it must at least be given some thought. That could have occurred if a significant increase in the population of a host organism, such as occurs with certain algal blooms, had taken place as a result of

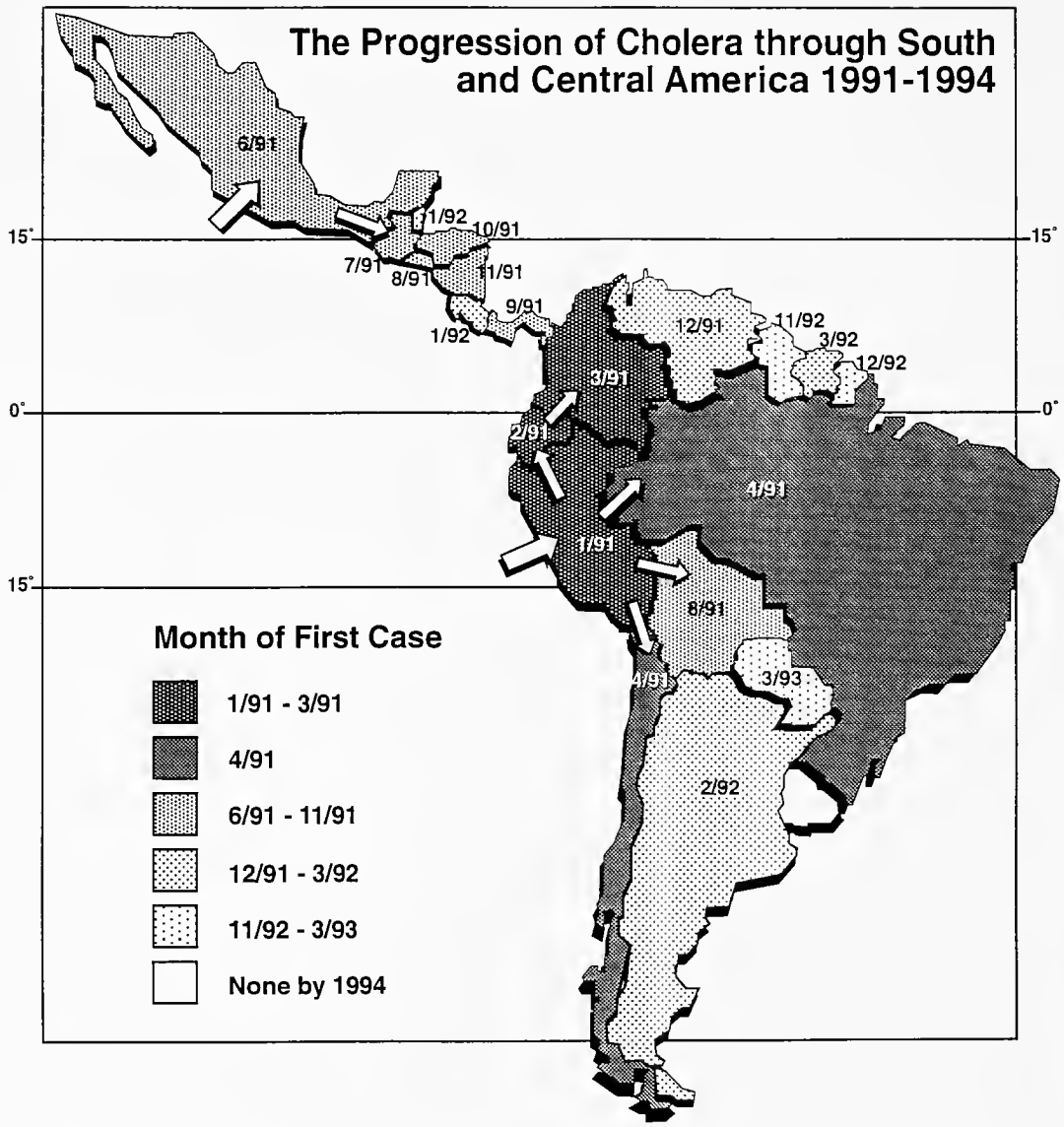

Fig. 2. Map of Central and South America showing the month of onset of the first reported case of cholera in each country. Countries are grouped according to month of first case.

especially favorable weather and nutritional conditions in the far-eastern south Pacific Ocean. That would be consistent with simultaneous appearance of the disease in a number of coastal Peruvian cities within a very few days (as well as the surprisingly high incidence in the initial outbreaks), since rapid amplification of the vibrio population in human hosts would not be required to explain the first generation of victims. The obvious argument against such a possibility is the absence of recognized cholera in Central America and South America for over a century. Let us return to that hypothesis after further examining the course of the Latin American dissemination from 1991 to 1994.

Regardless of the nature of the initial source of cholera vibrios, it is clear that suitable conditions for the successful introduction and subsequent spread of cholera were not confined to Peru, and it is doubtful that all of the same human interventions (or lack thereof) existed in all of the countries that were eventually visited by the disease. Within three months Ecuador, Colombia, Brazil, and Chile had reported outbreaks of cholera. By August 1991, Bolivia—the last of the countries that share a border with Peru—began to experience cholera in epidemic proportions. The spread of the disease throughout Latin America is shown in Figure 2. A curious happening not frequently noted was the appearance of cholera in southern Mexico in June of the same year, followed by a reasonably contiguous spread of the disease south through Central America during the latter half of 1991. Was that an independent introduction, again from an east-Asian freighter, or was it a second manifestation of an amplification of vibrios associated with an eastern Pacific planktonic bloom? Does it not seem curious that within six months, two successful introductions of pathogenic *Vibrio cholerae* would have occurred in only one region of the globe, when no such phenomenon had been observed during more than thirty years in which the Seventh Pandemic of cholera had been endemic in virtually all countries of east Asia except Japan? Perhaps a careful historical study of the numbers of east-Asian ships plying eastern Pacific waters and their practices of bilge handling would help establish the relative risk of such accidents having occurred during the preceding thirty years.

After making its Central American debut in the southeastern states of Mexico in June 1991, cholera subsequently spread to Guatemala, El Salvador, Panama, Honduras, and Nicaragua (in that order) from July to November of 1991. Whether that represented contiguous overland spread by infected persons discharging fecal vibrios into water supplies, or whether seaborne introductions took place in each country cannot be ascertained because all except Honduras have Pacific coastlines. The later introduction of cholera into Costa Rica and Belize in January 1992, after its appearance in Panama in the previous September, suggest that a simple country-to-country spread is not a satisfactory explanation.

By the end of 1991, when the Latin American epidemic had been in progress for about eleven months, a total of 299,332 cases and 3,993 deaths had been reported from fourteen countries in Central America and South America. Of them, 77 percent of the cases and 72 percent of the deaths occurred in Peru. By the end of 1994, some 963,171 cases and 9,552 deaths were reported from twenty of the twenty-one countries of Central America and South America (only Uruguay was spared). Of the four-year totals, 57 percent of the cases and 46 percent of the deaths were reported from Peru. The overall case-fatality rate for the entire Latin American experience during the first four years of the epidemic was 0.99 percent, a remarkably low figure for which the deliverers of health care in all of the Latin American countries should be congratulated.

In order to understand the epidemiology of cholera in Latin America, it is important to estimate the force of infection throughout the entire area. That force would determine the magnitude of conversion from immunologically susceptible to resistant individuals in the population. In order to determinate that force, an estimate of the frequency of inapparent and mild unreported infection is needed. (Until then, one

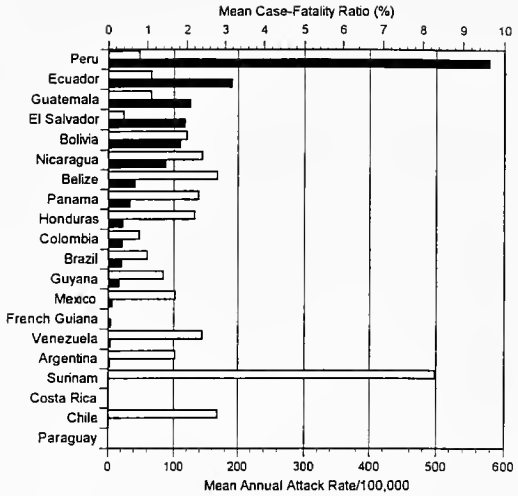

Fig. 3. Mean annual attack rates (solid bars) and mean case fatality ratios (open bars) in Central and South American countries, 1991–1994. Countries are listed in order of their mean annual attack rates for the four-year period.

can only extrapolate from earlier studies in other parts of the world.) Studies based on postepidemic serologic surveys have produced estimates of infection/case ratios as high as 100:1.[12] Estimates based on stool cultures in family and community contacts yielded ratios as low as 3:1. If the geometric mean of 17:1 is applied to the South American data, we see that in 1991 alone in Peru, about 3,900,000 persons—or 17 percent of the entire population of the country—were probably infected; by 1994, 9.3 million, or 40 percent, had been infected.

Although those are probably rough underestimations, we can be assured that large segments of the Latin American population have been and will be infected in succeeding years, and that regardless of the infection/case ratios that prevailed in the epidemic, the number of people infected and immunized far exceeded the reported cases. It can be assumed that those infected were rendered more resistant to reinfection than the previously uninfected members of their communities. That herd immunity will be a major factor in determining the incidence and age distribution of cholera in Latin America in the years to come. The other major factor will be the availability of vibrios in the environment for infection of the biologically and immunologically susceptible members of the community.

Figure 3 shows the average annual morbidity rates for the first four years of the Latin American epidemic in all of the countries affected. On the same graph the average case-fatality rates are shown. It is certainly recognized that those political units do not reflect the natural ecologic features that probably serve as the major determinants in the spread of disease. Unfortunately, population and disease data for such biomes are not available. Country and provincial data are all that exist, and they are useful for a rough tracking of the course of dissemination. Nevertheless, countries with very large areas—including Mexico, Brazil, and Argentina—all had low overall attack rates that did not accurately reflect the higher rates that occurred in restricted parts of their respective territories.

By March of 1993, a little over two years after the first cases were recognized in Peru, all countries of Central America and South America except Uruguay had been seeded. The South American countries followed a roughly centrifugal pattern of spread from the initial major focus in Peru. The Central American spread was roughly linear from Southern Mexico toward Panama. The first cases appeared in Venezuela, Argentina, and Surinam in the end of 1991 or in the early months of 1992. Guyana, French Guiana, and Paraguay did not experience their first cases until nearly a year later. No cases were reported from the island nations of the Caribbean throughout the first four years of the epidemic. That would suggest that all introductions were from the Pacific shores of the continent, regardless of the nature of the source.

The generally low case-fatality rates were a striking feature of the entire American experience with cholera. Figure 3 clearly shows that all of the countries that had higher morbidity rates enjoyed remarkably low case-fatality rates. In Peru, with an average annual morbidity rate of 580/100,000, the average case-fatality rate was about 0.8 percent. Those values were repeatedly confirmed by outside observers, attesting to the excellent clinical management of cases in the face of overwhelming caseloads, especially in the first year of the epidemic. The high case-fatality rate for Surinam is of little significance since the total number of cases was only twelve.

In order to examine in more detail the true nature of the progression and seasonal distribution throughout the four-year period, monthly morbidity rates (cases/100,000 population/month) were calculated for ten selected countries, five in South America and five in Central America. The data are shown in Figure 4. In each country the seasonal peaks tended to occur in the same part of the year each year. During the forty-eight months of 1991–1994, it was possible to identify fifty-two distinct seasonal peaks in seventeen of the countries involved. When those countries were further divided into two groups according to latitude, it turned out that in the twelve countries whose landmass lies predominantly north of the equator, most of the peaks occurred between January and June. In the six countries lying predominantly south of the equator, most of the peaks occurred between July and December. Those data are depicted in Figure 5. The tendency can also be seen in Figure 4. In the five South American countries, peaks occurred predominantly in the early part of each year. In the five Central American countries, peaks occurred predominantly in the latter half of the year. The incidence data shown in Figure 4, combined with this difference in seasonal predominance, suggest that environmental factors related to hours of sunlight and perhaps associated temperature and climatic factors played an important role in determining the timing of the annual peaks. In other words, during the first four years of that neotropical epidemic—regardless of the month of introduction into each country—the seasonal cycles tended to settle into a cyclic pattern of late-summer and fall epidemics even though the vast bulk of the epidemic occurred in populations living between the Tropics of Cancer and Capricorn where temperature extremes do not occur. In fact, most disease occurred between the 15 N and 15 S latitudes, where seasonal temperature differences are even less pronounced.

These observations tend to support the notion that after the initial introduction of vibrios into a region, intrinsic environmental factors played the most influential role in determining seasonal fluctuations in the available numbers of infectious vibrios in the environment and hence the number of cases. Herd immunity and sanitary measures probably influenced the magnitude of those peaks to some extent but not their distribution in time and place. If immunity and human intervention were the major epidemiologic determinants of incidence, one should expect a gradual fall in incidence through all seasons after an initial single epidemic peak. The data depicted in Figure 4 suggest, on the other hand, a tendency toward diminishing annual peaks following a maximum first-year peak. Such a pattern occurred in seven of the ten countries shown in Figure 4.

A more detailed examination of the annual outbreaks in Chile is instructive. Because

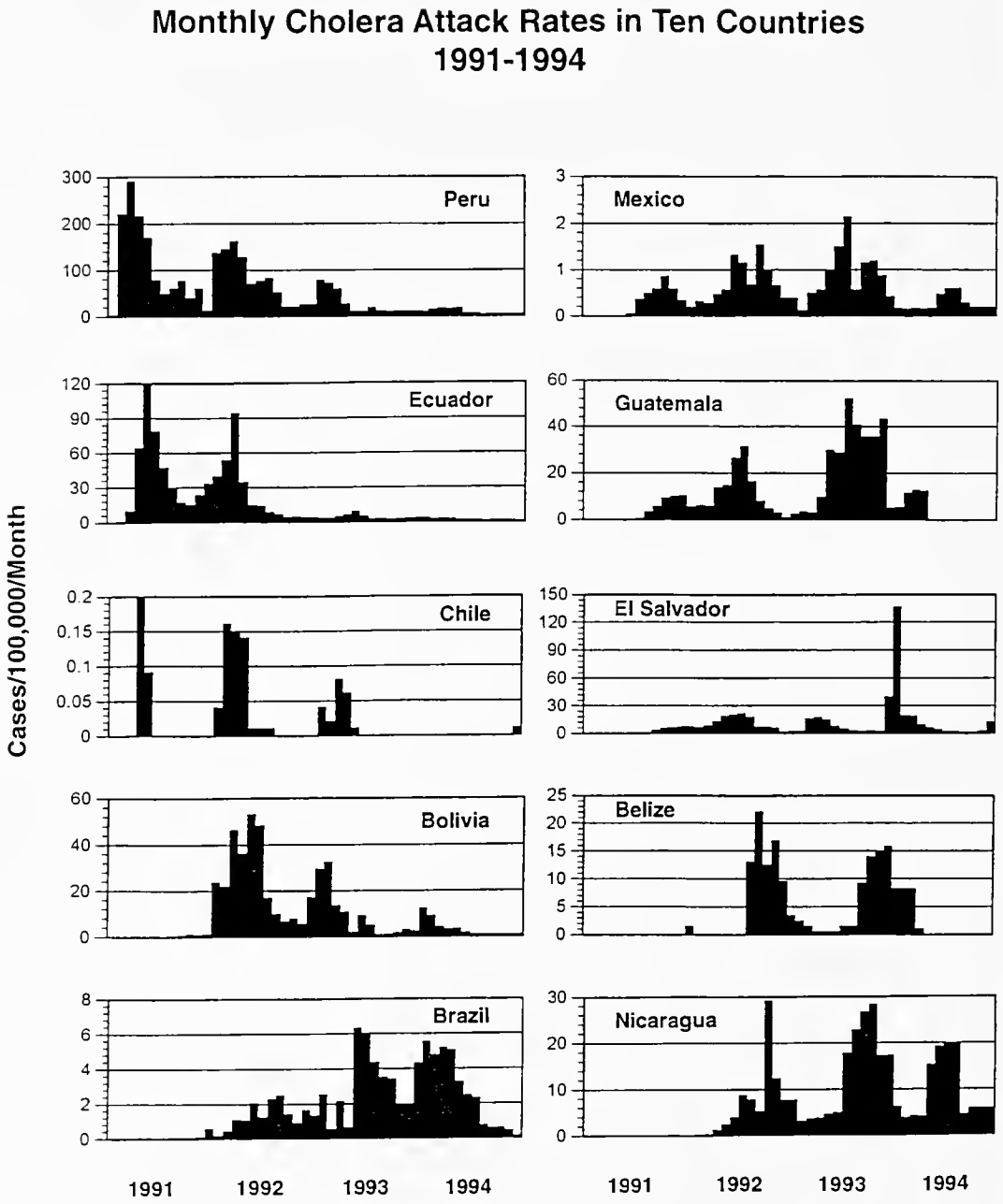

Fig. 4. Monthly cholera morbidity rates (cases/100,000/month) in ten selected countries during the first four years of the cholera epidemic in Central and South America.

of the low incidence there and perhaps because of better conditions of environmental hygiene, the overall incidence during the four years of observation was very low. Yet the disease appeared in a series of very well separated sharp autumn peaks separated by periods in which no disease was reported. The first reports were in mid-April in 1991, and the outbreak ended by mid-May of that year. In all, forty cases were reported. Cholera then seems to have disappeared entirely until January of 1992, in the Chilean midsummer, when a six-month outbreak comprising seventy-one cases occurred with a peak in February, March, and April. The disease again disappeared until January 1993, when another small outbreak of twenty-nine cases again occurred between January and May of that year. In 1994 only one case was reported in late December. Thus, three distinct prolonged periods of several months during which cholera seems to have disappeared were punctuated by four separate small outbreaks.

Was cholera reintroduced into northern Chile on four separate occasions, or did the temporal distribution suggest an environmental reservoir, perhaps in association with the microflora or fauna of local freshwater bodies that was reactivated in some manner during the warmer months of each year? Perhaps, in order to disclose the manner in which pathogenic strains of *Vibrio cholerae* can be maintained in the nonhuman environment, it would be wise to examine more carefully such areas as Chile in which a year-round human-to-human passage of cholera vibrios cannot be sustained because of a relatively high level of personal and community sanitation.

There have been a number of unexplained events in the history of cholera that are bound to raise the antennae of the curious. One of those has been the uncanny tendency of disease incidence to rise simultaneously in distant and apparently unconnected regions of the globe. That was again demonstrated when ten African nations reported over 45,000 cases with 3,488 deaths during the first six months of 1991, the year in which the South American epidemic began and in which the population suffered its highest incidence.[13] Cholera had become permanently endemic in much of central Africa in the early 1970s; in the next two decades it can be assumed that much of the African population had been immunized by inapparent or manifest infection. Yet, for unexplained reasons, the same population (of course, augmented annually by immunologically-naive newborns) experienced a marked increase in incidence and mortality during the same six months that the Latin American epidemic took its greatest toll. The strains of *Vibrio cholerae* responsible for the two epidemics were different.

Are there global climatic or other environmental influences at work that significantly alter the numbers of infectious organisms available for consumption by the human populations in different parts of the globe at the same time? Another riveting fact was strikingly demonstrated by the concurrence of those two equatorially-centered epidemics. In spite of the two decades of endemic cholera that much of central Africa had experienced between 1970 and 1990, case-fatality rates in African countries ranged from 6 percent to as high as 30 percent in the great flurry of cholera activity in 1991. In South America, on the other hand, where the population had not experienced the immunizing effects of two decades of endemic cholera, case-fatality rates ranged from 1 percent to 2 percent, with countries suffering the highest morbidity rates enjoying the

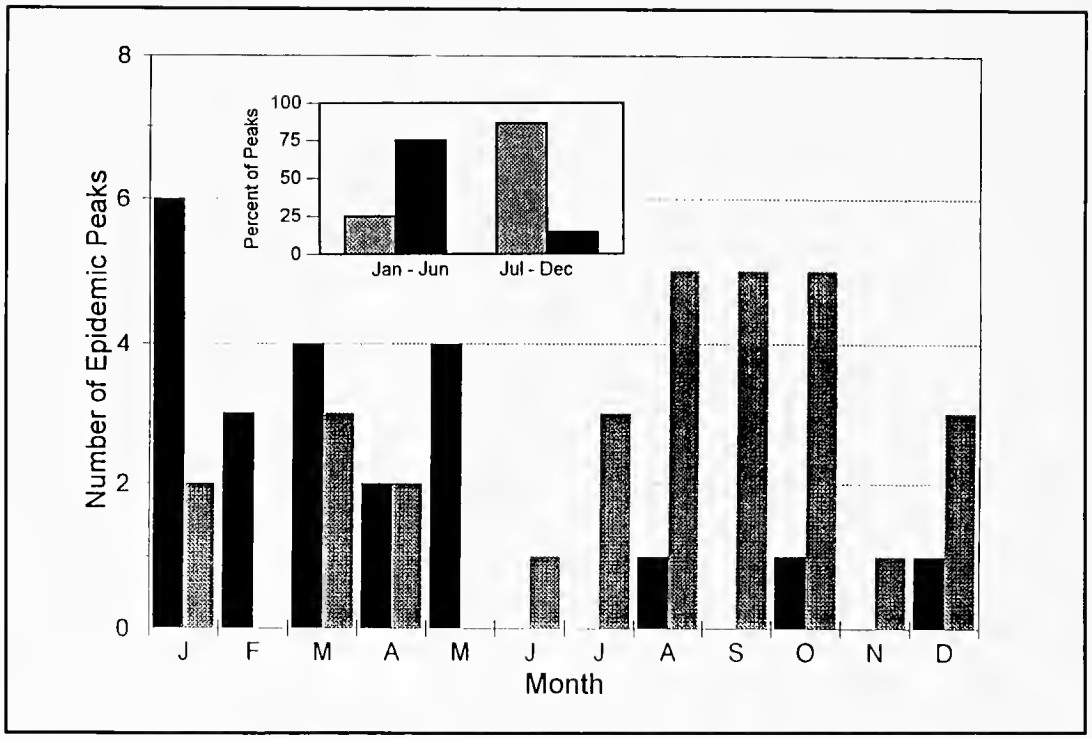

Fig. 5. Distribution of epidemic peaks by month in eighteen countries according to latitude. Solid bars indicate south; open bars indicate north.

lowest mortality. Can all of the difference in disease outcome be attributed to superior management of cases by the health care deliverers of South America and Central America? Had the case-fatality ratios been reversed, might we not have been tempted to attribute the difference to longer experience in treating severe cholera, possibly in concert with a higher level of herd immunity? We are left without satisfactory answers.

Throughout medical history, the tendency to discover the source of particularly loathsome and feared disease in a foreign and unfamiliar nation has always been with us. The French pox, the Spanish influenza, and Asiatic cholera come to mind. When the first case of cholera in the United States in the Seventh Pandemic occurred in Texas in 1973, assumptions of introduction by Vietnamese immigrants were immediately voiced. Modern techniques of strain identification rapidly disabused us of that notion and demonstrated that the organism responsible for that case was an indigenous strain of *Vibrio cholerae* that resides as a member of the autochthonous flora of United States Gulf Coast estuarine waters, and that it could be readily distinguished from Asian strains and from the strains responsible for the recent Latin American epidemic.[14] Moreover, it was shown that those autochthonous strains enjoyed a special association with shellfish and large and small crustacea, upon which they can achieve much larger populations than in open water

because of their peculiar use of certain enzymes that allow them to profit from their propinquity with those animal hosts. Does the current Latin American epidemic provide us with any evidence for or against the proposition that it, too, could have resulted from the activation of a hitherto dormant population of pathogenic vibrios in this hemisphere rather than an importation from China? I believe that at the present time the question cannot be answered. But the evidence suggests that multiple introductions occurred along the Pacific Coasts of Central America and South America, from Mexico to Peru, and that those introductions could at least as readily have been achieved through the amplification of vibrios on an algal bloom as from a single or multiple introductions from bilge from an Asian freighter. We must keep an open mind in order to arrive at an answer to the remaining and most perplexing problem in cholera biology.

A Natural Home

A major innovation in thinking about the natural history of cholera arose just prior to the onset of the current Seventh Pandemic. For the first time, serious questions were asked about the long-held notion that the human small bowel is the natural reservoir of the cholera vibrio, the major locus in nature where the microorganism persists. The conventional notion that had prevailed since Robert Koch discovered the cholera vibrio in the ileal mucosa of patients who had died of the disease, required either an endless human chain of transmission or a prolonged, silent carrier state similar to the decades-long carrier state in the gallbladder of *Salmonella typhi* carriers. Otherwise, how could one explain the repeated disappearances and recrudescences after many disease-free months or years? But tireless efforts to demonstrate such carriers in cholera had failed.

Credit must be given to T. Aiden Cockburn and James G. Cassanos for being among the first to systematically study environmental factors that might account for the striking seasonal variations noted in endemic cholera in Bengal, a major residuum of the disease in the interepidemic period preceding the onset of the Seventh Pandemic.[15] They postulated that the reason for perennial persistence of the disease in Bengal was not the persistence of infection in the urban population of Calcutta but rather the persistence of cholera vibrios in village waterponds (tanks) in rural Bengal. The essence of their thinking is best revealed in the following quotation:

> We suggest that in Bengal the endemic infection is primarily rural, and that the Calcutta urban region is of secondary importance. Many other cities in the world with large populations and overcrowding like Calcutta have experienced cholera epidemics, but in these always the infection has died out. London in the mid-19th century days of John Snow closely resembled Calcutta with its masses of people, insanitary slums, and cholera-infected river, but the vibrio failed to establish a permanent foothold. Calcutta has what the other cities do not have, a surrounding countryside in which cholera always exists.[16]

Those studies demonstrated a clear correlation between the incidence of cholera in rural villages, and sunlight and pH in village ponds, suggesting that the ponds were the chief reservoir and means of spread of the vibrio. They proposed that in hot, dry weather algae in the ponds raised the pH to high levels that afford cholera vibrios a selective advantage over other organisms. The implication is that cholera vibrios are capable of surviving indefinitely outside the human

host in an appropriate nonhuman environmental niche, although Cockburn and Cassanos did not say so explicitly. Nor did they explicitly postulate the amplification of vibrio populations on the surface of or in intimate association with algae, but rather they implied that the vibrios were free-swimming autochthonous members of the pond flora and that vibrio populations rose and fell with pH changes.

More recently Sirajul Islam and David Bradley and their colleagues, after conducting studies in ponds in Bangladesh in the same areas studied by Cockburn and Cassanos three decades earlier, have proposed an even more central and crucial role for blue-green algae (Cyanobacteria) in the ecology of cholera.[17] They hypothesized that cholera vibrios survive inside the nutrient-rich mucilaginous sheath of blue-green algae for long periods of time, where they enjoy a symbiotic relationship in perpetuity. Rapid amplification of vibrio populations occurs during algal blooms followed by release from the mucilaginous sheath during reproduction and disintegration of algal cells. They postulated that the internal multiplication within the mucilaginous algal sheath may explain previous failures to recover cholera vibrios from water samples that have been rendered plankton-free before culture. The authors further proposed that the salinity requirements of *Vibrio cholerae* can be reduced when they find themselves inside the highly specialized environment of the mucilaginous algal sheath. That might help to explain how the distribution of cholera vibrios can sometimes be extended to freshwater environments instead of being restricted to estuarine waters.

Meanwhile, another challenge to the "ultimate human reservoir" concept in cholera epidemiology was led mainly by Rita Colwell and her many colleagues and students at the University of Maryland. Their work arose from a background of studies on the ecology of *Vibrio parahaemolyticus* in Chesapeake Bay, where they discovered that organism (and later *Vibrio cholerae*) was capable of first colonizing the exoskeletons of copepods and then "hibernating" in a nonculturable but viable state for long periods. Colwell postulated that *Vibrio cholerae* is an autochthonous inhabitant of moderately saline, estuarine waters in several reservoir zones of the world in which they can remain in a dormant state for many years. In the dormant state, the vibrios are greatly reduced in size and can be cultivated only under special conditions.[18] The seemingly oxymoronic appelation of "nonculturable but viable" organisms has created bewilderment in some quarters, but now that the terms of reference have been established and reasonably defined, the concept has become a valuable and important contribution to our understanding of vibrio ecology.

Thus, many of the epidemiological questions raised by the current epidemic in Central America and South America had already been addressed by several groups of investigators. The advent of widespread dissemination in a "new" continent has provided fresh opportunities to define the natural history of the cholera vibrio and to determine its "natural home." Until the natural habitat(s) of the microbe can be fully defined—both qualitatively and quantitatively—the natural history of cholera will remain clouded in mystery.

An Immune Evasion

Another event in the saga of cholera occurred in late 1992, when a disease that was clinically indistinguishable from typical

cholera appeared in India and Bangladesh. Laboratory technicians accustomed to the serological identification of cholera vibrios by agglutination with antisera immediately recognized that although the organisms isolated from patients in the outbreak had all the expected properties of cholera vibrios, they failed to agglutinate with the standard anti-O1 sera.[19]

Ever since the agglutinating system was devised, all cholera vibrios causing epidemic disease had belonged to a single serogroup that was arbitrarily assigned the number "1." Because the antigen involved is a surface, or O, antigen on the bacterial cell wall, the serogroup of all epidemic and pandemic cholera strains thus far isolated had been designated "O1." In the intervening years, 138 O antigens had been discovered, and all of the strains from O2 to O138 had been considered "non-O1" *Vibrio cholerae*. If they occasionally caused disease, it was always sporadic, usually occurred in small, nonspreading outbreaks, and never displayed the character of "dispersiveness" that was the major, ineffable but critical property of the epidemic O1 strains.[20] Because the organism causing the outbreak on the shores of the Bay of Bengal in December 1992 possessed a hitherto unknown surface antigen, it was given the moniker Bengal O139.

Earlier studies had clearly shown that a number of the non-O1 strains of *Vibrio cholerae* that had been isolated from the environment and from occasional patients and small outbreaks of diarrhea throughout the Seventh Pandemic could occasionally produce the same enterotoxin molecule as did the O1 strains.[21] Therefore, in retrospect, it should not have been surprising that some day one of those toxinogenic strains bearing a new or different somatic or surface lipopolysaccharide (specifically, the O139 antigen) could somehow acquire that elusive property of dispersiveness, sometimes referred to as epidemic potential, that apparently was not possessed by any of the previously known non-O1 strains. Bengal O139 appeared to be just such a strain.

Bengal O139 spread rapidly throughout most of India, Bangladesh, Pakistan, Sri Lanka, Nepal, Afghanistan, Thailand, China, and Malaysia. Imported cases were reported in Europe and the United States, but there was no local spread. Its distribution in the populations it infected confirmed the suspicions of many of those who had worked for decades on the immunology of cholera—that acquired immunity depended largely on the antibodies directed against the major somatic antigens rather than on antitoxic immunity. When Bengal O139 entered communities in India and Bangladesh that had experienced endemic O1 cholera for decades, it behaved like a new disease; most cases were found in adults, just as had been true of O1 cholera in Latin America in 1991. Since the enterotoxins of O1 and O139 are identical, the difference in age distribution suggests that the preexisting antitoxic immunity engendered by long-standing endemic O1 cholera offered no protection. One could anticipate that if O139 becomes permanently endemic in the Indian subcontinent it will gradually shift to a childhood disease as O1 cholera has done.

Conclusion

The Seventh Pandemic has brought about a much greater understanding of the way that the bacterium known as *Vibrio cholerae* can produce disease in the individual human being. We have learned rather successfully how to treat patients who are its victims. Our knowledge of immunity is still

insufficient to produce a really effective vaccine, however. We are just beginning to understand the complex ecology of the bacterium, and we are slowly but surely moving toward the realization that its tempestuous encounters with our species may be a rather incidental—even inconsequential—part of its life history in the grand scheme of things.

In our anthropocentric view, this notion may be difficult to accept, but it is likely to be true. Its real home is more likely to be upon and within a variety of marine, estuarine, or even freshwater small plants, animals, and other bacteria. The remote and ancient origins of its virulence factors, and their unique affiliation with the human species, remain a profound mystery. Even more remote from our understanding is the physical basis for that quintessential property of those special clones of the organism that render them capable of rapid spread through a human population, namely the property of dispersiveness.

What, then, is the outlook for cholera in the twenty-first century? The enlightenment and experience we have gained during the first thirty-four years of the Seventh Cholera Pandemic make it clear that the most effective means of reducing the effects of cholera's ravages are twofold: (1) increase the availability of clean water protected from fecal contamination in countries where these amenities do not yet exist; and (2) continue relentlessly to improve and sustain the training of health professionals in the proper use of both oral and parenteral water and electrolyte replacement therapy for all kinds of diarrhea. A keen level of alertness and action in both of those areas has the added virtue of reducing morbidity and mortality from all infectious diarrheal diseases, not just cholera. Moreover, safe and dependable water represents one of the major hallmarks of civilization that will enhance the quality of life for all. Fear of cholera spearheaded the nineteenth-century movements that established boards of health and sanitary codes in the societies we now call "developed." Let the process continue apace at the highest priority in the next century. Unfortunately, the miserably low rate of progress in this area in the poor countries of the world in the last half-century gives one little reason for optimism that improvements will be sufficient to avert continuing outbreaks of cholera in the decades to come. The incidence in Asia, Africa, and South America will be inversely related to the success these countries have in providing clean water and food to their citizens.

Better understanding of the immune mechanisms by which recovered victims of cholera are rendered resistent to reinfection will almost certainly lead to the development of an effective vaccine within the next decade. It would be naive, however, to expect, regardless of the success of such a vaccine in protecting the individual, that vaccine delivery systems will be able to sustain the massive and perpetual worldwide immunization programs that would be necessary to control or prevent a disease caused by an organism that cannot realistically be eradicated from a permanent, natural, nonhuman environment reservoir. We already know that cholera is robbed of its dispersive power when it enters communities that provide clean water and some means of interrupting the fecal-oral transmission chain. During the past three decades, cholera has utterly failed to spread in the United States, Japan, Australia, and western Europe in spite of repeated introductions, and a permanent, autochthonous estuarine reservoir along the gulf coast of the United States.

We also already know that good treatment leads to 99 percent recovery. The priorities, therefore, should be clear. An acceptable level of cholera control can clearly be achieved and maintained without eradication of the causative bacterium from the planet and without universal vaccination, if societies have the will to provide for these basic necessities.

♦

Notes

1. John Snow, *On the Mode of Communication of Cholera*, 2nd ed. (London: Churchill, 1855; reprinted, New York: Commonwealth Fund, 1936).

2. R. Koch, "Die Conferenz zur Erorterung der Cholerafrage," *Deutsche medizinische Wochenschrift* 10 (1884): 499.

3. Koch's *Postulates* as translated in G. S. Wilson and A. A. Miles, *Topley and Wilson's Principles of Bacteriology, Virology, and Immunity*, 6th ed., 2 vols. (Baltimore: Williams and Wilkins Company, 1975). The three postulates are: (1) The microorganism should be found in all cases of the disease in question, and its distribution in the body should be in accordance with the lesions observed; (2) The microorganism should be cultivated outside the body of the host, in pure culture, for several generations; and (3) The organism so isolated should reproduce the disease in other susceptible animals.

4. R. B. Hornick, S. I. Music, R. Wenzel, R. Cash, J. P. Libonati, M. J. Snyder, and T. E. Woodward, "The Broad Street Pump Revisited: Response of Volunteers to Ingested Cholera Vibrios," *Bulletin of the New York Academy of Medicine* 47 (1971): 1181–91.

5. J. P. Craig, "The Enterotoxic Enteropathies," *Symposia of the Society for General Microbiology* 22 (1972): 129–55; J. P. Craig, "A Survey of the Enterotoxic Enteropathies: In Cholera and Related Diarrheas," *43rd Nobel Symposium . . . 1978* (Basel: Karger, 1980), 15–25; J. P. Craig, "The Vibrio Diseases in 1982: An Overview," in *Bacterial Diarrheal Diseases*, ed. Y. Takeda and T. Miwatani (Tokyo: KTK Scientific Publishers, 1985), 11–23; J. P. Craig, "The Search for the Cause of Cholera Since Robert Koch's Discovery of the Kommabacillus," in Vibrio cholerae *and Cholera*, ed. Y. Takeda and S. Kuwahara (Tokyo: KTK Scientific Publishers, 1988), 33–45; J. B. Kaper, J. G. Morris, Jr., and M. M. Levine, "Cholera," *Clinical Microbiology Reviews* 8 (1995): 48–86.

6. S. N. De, "Enterotoxicity of Bacteria-free Culture Filtrate of *Vibrio cholerae*," *Nature* 183 (1959): 1533.

7. A. M. Kamal, "The Seventh Pandemic of Cholera," in *Cholera*, ed. D. Barua and W. Burrows (Philadelphia: W. B. Saunders, 1974), 1–14.

8. F. Chen, G. M. Evins, W. L. Cook, R. Almeida, N. Hargrett-Bean, and K. Wachsmuth, "Genetic Diversity among Toxigenic and Nontoxigenic *Vibrio cholerae* O1 Isolated from the Western Hemisphere," *Epidemiology and Infection* 107 (1991): 225–33.

9. R. Pollitzer, *Cholera*, WHO Monograph Series No. 43 (Geneva, 1959), 1019.

10. World Health Organization, *Weekly Epidemiological Record* (Geneva).

11. C. Anderson, "Cholera Epidemic Traced to Risk Miscalculation," *Nature* 354 (1991): 255

12. C. B. Gerichter, I. Sechter, J. Cohen, and A. M. Davies, "A Serological Survey for Cholera Antibodies in the Population of Jerusalem and Surroundings," *Israel Journal of Medical Science* 9 (1973): 980.

13. WHO Press, World Health Organization, Office of Information, Geneva, Press Release WHO/64, Dec. 30, 1991.

14. Chen et al., "Genetic Diversity."

15. T. A. Cockburn and J. G. Cassanos, "Epidemiology of Endemic Cholera," *Public Health Reports* 75 (1960): 791–803.

16. Ibid.

17. M. S. Islam, B. S. Drasar, and D. J. Bradley, "Long-term Persistence of Toxigenic *Vibrio cholerae* O1 in the Mucilaginous Sheath of a Blue-Green Alga, *Anabaena variabilis*," *Journal of Tropical Medicine and Hygiene* 93 (1990): 133–39; M. S. Islam, B. S. Drasar, and R. B. Sack, "Probable Role of Blue-green Algae in Maintaining Endemicity and Seasonality of Cholera in Bangladesh: A Hypothesis," *Journal of Diarrhoeal Disease Research* 12 (1994): 245–56.

18. R. R. Colwell, J. Kaper, and S. W. Joseph, "*Vibrio cholerae, Vibrio parahaemolyticus* and Other Vibrios: Occurrence and Distribution in Chesapeake Bay," *Science* 198 (1977): 394–96; A. Huq, R. R. Colwell, R. Rahman, A. Ali, M. A. R. Chowdhury, S. Parveen, D. A. Sack, and E. Russek-Cohen, "Detection of *Vibrio cholerae* O1 in the Aquatic Environment by Flourescent-Monoclonal Antibody and Culture Methods," *Applied Environmental Microbiology* 56 (1990): 2370–73; R. R. Colwell and W. M. Spira, "The Ecology of *Vibrio cholerae*," in *Cholera*, ed. D. Barua and W. B. Greenough III (New York: Plenum Publishing Corporation, 1992), 107–27; R. R. Colwell and A. Huq, "Vibrios in the Environment: Viable But Nonculturable *Vibrio cholerae*," in *Vibrio cholerae and Cholera: Molecular to Global Perspectives*, ed. I. K. Wachsmuth, P. A. Blake, and O. Olsvik (Washington, D.C.: ASM Press, 1994), 117–133.

19. Cholera Working Group, International Centre for Diarrhoeal Diseases Research, Bangladesh, "Large Epidemic of Cholera-like Disease in Bangladesh Caused by *Vibrio cholerae* O139 Synonym Bengal," *Lancet* 342 (1993): 387–90; World Health Organization, *Weekly Epidemiological Record*.

20. The term "dispersiveness" as applied to the quintessential feature of epidemic cholera seems to have been introduced by Major Greenwood in his chapter on cholera in *Epidemics and Crowd Diseases* (London: Williams and Norgate, Ltd., 1935), 165. No better word has been proposed. It is not completely clear whether he borrowed the word from a German equivalent used by the German epidemiologist Sticker or introduced it himself. Greenwood's words of 1935 are particularly apt: "Cases of cholera in its deadly form were accurately described in the Hippocratic collection; epidemics of cholera occurred, for instance, in Alkmar in 1548, in Nîmes in 1645, in London in 1669 and 1676, in Vienna in 1786, before the nineteenth century. But epidemiologists agreeing in little else agree that the particular manifestations of cholera which showed themselves in Europe after Waterloo differed epidemiologically from anything which had been seen before. This difference may be summarized in a phrase as a difference in dispersiveness. 'What,' writes Sticker, 'was new in the history of Indian cholera [he is writing about the events of 1817] and rightly caused apprehension there as well as here was the further intelligence that this destructive epidemic no longer confined itself to a particular area and at the accustomed season of the year appeared simultaneously in several places, but set itself in motion, under the influence of some mysterious impulse began to travel, and, without paying attention to the season of the year, attaching itself to the lines of human intercourse, spread widely in various directions, exacting everywhere hecatombs of victims.'" For those interested in a provocative discussion of the epidemiology of cholera before the Seventh Pandemic, Greenwood's chapter will prove rewarding.

21. J. P. Craig, K. Yamamoto, Y. Takeda, and T. Miwatani, "Production of Cholera-like Enterotoxin by a *Vibrio cholerae* non-O1 Strain Isolated from the Environment," *Infection and Immunity* 34 (1981): 90–97.

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The Tuberculosis Story: From Koch to the Year 2000

Mahfouz H. Zaki and Mary E. Hibberd

For decades, tuberculosis mortality and morbidity in most countries had been declining even before the recognition of the tubercle bacillus by Robert Koch in 1882. That decline was attributed in part to a concomitant improvement in the environmental-socioeconomic-sanitary complex and to a gradual reduction in the infection reservoir.

In 1941 Louis Dublin of the Metropolitan Life Insurance Company predicted that tuberculosis would be eradicated by 1960.[1] "No Tuberculosis by 1960" was the slogan of the National Tuberculosis Association for decades to come. With the introduction of streptomycin in 1948 and isoniazid and para-aminosalicylic acid in 1952, many public health and preventive medicine experts predicted the eventual elimination of tuberculosis as a public health problem within a decade or two. In 1958 James Perkins issued a serious challenge for a "formal concentrated program of eradication of tuberculosis from the whole face of the earth."[2] The following year, the Arden House Conference on Tuberculosis in Harriman, New York, considered the eradication of tuberculosis a prime objective.[3]

Literally, eradication of an infection means the wiping out of the infection and the extinction of the responsible pathogen. As the name implies, eradication is an absolute process and not a relative goal. In other words, it follows an "all-or-none" phenomenon. Mathematically, an infection will reach the baseline if the regression slope of the trend remains negative on successive years. The rapidity with which the infection will be eradicated depends upon the magnitude of the regression slope.

A question frequently asked about public health is: Has any disease actually been radically eradicated? In principle, is it possible to reduce an infection to the degree of extinction or eradication? Theoretically speaking, the answer is yes. Certain prerequisites, however, have to be met. The disease should have no carrier state or animal reservoir, should be easily diagnosed, and should have easily deployable prophylactic tools available. Very few diseases can satisfy such criteria, with the notable exceptions of smallpox and measles.

Experience gleaned from many infectious diseases has shown that once the morbidity of a disease reaches a very low level, a residual infection usually persists in the population and a state of equilibrium becomes established between the agent, host, and environmental components of the disease process. Although malaria eradication programs have been carried out in many parts of the world for more than six decades, malaria cases are still reported sporadically in

the so-called eradicated areas. Some of those cases are imported, while others are indigenous.

The United States and the Scandinavian countries started extensive eradication programs for bovine tuberculosis in the late 1930s and early 1940s. Slaughtering of infected cattle was an essential feature of the program, but—in spite of that draconian measure—bacteriologic eradication was not achieved. The disease did, however, reach a very low level, which has been static for several years and may remain so for decades to come. F. L. Soper, in his superb discussion of the problems encountered in the epidemiology of a disappearing or retreating disease, refers to the hidden foci of infection, the unrecognized methods of transmission, and the erratic behavior of residual infections—all of which present real problems in the eradication process.[4]

Some investigators, realizing the difficulty of achieving bacteriologic eradication, prefer to use the phrase "eradication as a public health problem," which denotes nothing but substantial control. Omitting the problem of semantics and assuming a more realistic attitude (thus substituting control for eradication), let us review in brief where we stand in the control of tuberculosis, as well as the far-fetched goal of elimination. The indices that describe the experience of a population with tuberculosis are the mortality rates, the morbidity rates, and the prevalence of tuberculous infection in the community.

Mortality Rates

For most infectious diseases, including tuberculosis, mortality statistics have been considered relatively reliable measures for international comparisons. Such comparisons are doubtless subject to many sources of error, particularly the extent of completeness of reporting and the criteria used to define a tuberculosis death. The well-known pattern of tuberculosis mortality among males recognized in the early decades of this century was characterized by relatively high mortality among children under the age of four years, followed by a very low rate in the age group between five and fourteen years. The rate gradually rose to a peak between twenty-four and thirty-six years, followed by a plateau or slight decline until the age of fifty or fifty-five, a gradual rise until seventy-five or eighty, and a final slight decline.

Tuberculosis morbidity and mortality rates among the young age groups have shown marked decline in most countries during the past six decades. That decline, however, has not been maintained for older segments of the populations. If accidents, acts of war, homicide, suicide, and malignancies are excluded, tuberculosis is still one of the leading causes of death in the fifteen to forty-four age group.

Estimates of tuberculosis deaths in various countries have been calculated by the World Health Organization (WHO). During 1990 an estimated 2.53 million deaths from the disease occurred worldwide, of which 116,000 were associated with human immunodeficiency virus (HIV) infection. Should the current trend continue, the WHO estimates that about 3.5 million deaths will occur in the year 2000, approximately 500,000 of which will be associated with HIV. Predictions are that about half of the TB-HIV deaths will occur in sub-Sahara Africa.[5] Table 1 shows estimates of tuberculosis deaths in the years 1990, 1995, and 2000, including those that would be HIV-related. Most of the burden will be carried by Southeast Asia, Africa, and the Western Pacific regions. The percentage of HIV-associated deaths is ex-

pected to rise from 4.6 percent in 1990 to 14.2 percent in the year 2000.[6]

With the emergence of AIDS in the early 1980s, the preexisting mortality peak among the elderly has been accompanied by a new peak in the twenty to forty-nine age group. By 1990 in the United States, 54.2 percent of deaths from tuberculosis in that age group also had AIDS on the death certificates. A sizeable difference has also been noted in the death rates between white and nonwhite patients. Of AIDS deaths in 1990, 1.6 percent of whites died with tuberculosis, compared to 4.7 percent of blacks and 4.7 percent of Hispanics.[7]

Co-infection with HIV has added another dimension to the tuberculosis dilemma. Nosocomial transmission of the *Mycobacterium tuberculosis* (*M. tuberculosis*) became a serious problem in the last decade among hospitalized AIDS patients. That problem was further compounded by the emergence of multidrug-resistant (MDR) strains that required prolonged therapy and the possible lengthening of the communicability period.

Table 2 shows tuberculosis mortality and morbidity in the United States from 1955 to 1993. The mortality rate per 100,000 dropped from 9.1 in 1955 to 0.6 in 1993, a decrease of

Table 1
Estimated Total Tuberculosis Deaths and the Total HIV-Related Tuberculosis Deaths, 1990–2000

REGION	1990	1995	2000
Southeast Asia	T 1,087,000 HIV 23,000	T 1,225,000 HIV 88,000	T 1,383,000 HIV 200,000
Western Pacific[1]	T 644,000 HIV 7,000	T 716,000 HIV 11,000	T 789,000 HIV 24,000
Africa	T 393,000 HIV 77,000	T 581,000 HIV 150,000	T 823,000 HIV 239,000
Eastern Mediterranean	T 249,000 HIV 4,000	T 290,000 HIV 6,000	T 338,000 HIV 15,000
Americas[2]	T 114,000 HIV 4,000	T 121,000 HIV 9,000	T 129,000 HIV 32,000
Eastern Europe and others[3]	T 29,000 HIV 200	T 30,000 HIV <600	T 32,000 HIV <900
Western Europe and others[4]	T 14,000 HIV <500	T 14,000 HIV 1,000	T 15,000 HIV 2,000
All Regions	T 2,530,000 HIV 116,000	T 2,977,000 HIV 266,000	T 3,509,000 HIV 500,000
Percentage HIV attributed	4.6	8.9	14.2

SOURCE: Centers for Disease Control and Prevention, "Estimates of Future Global Tuberculosis Morbidity and Mortality," *Morbidity and Mortality Weekly Report* 42 (1993): 961–64.

1. Includes all countries of WHO except Japan, Australia, and New Zealand.
2. Includes all countries of WHO except the United States and Canada.
3. Includes all independent states of the former Soviet Union.
4. Western Europe and the United States, Canada, Australia, Japan, and New Zealand.

Table 2
Tuberculosis Morbidity and Mortality in the United States, 1955–1993

YEAR	CASES		DEATHS	
	Number	Rate per 100,000	Number	Rate per 100,000
1955	77368	46.9	15016	9.1
1960	55494	30.8	10866	6.0
1965	49016	25.3	7934	4.1
1970	37137	18.3	5217	2.6
1975	33989	15.9	3333	1.6
1980	27749	12.3	1978	0.9
1985	22201	9.3	1752	0.7
1990	25701	10.3	1810	0.7
1993	25287	9.8	1530	0.6

93 percent. In the United States, as in most developed countries, the tuberculosis problem has been mostly concentrated in such large urban centers as New York City. The tuberculosis mortality rate in New York City in 1955 was 13.9 per 100,000; in 1993 it was 2.3 per 100,000. The latter rate is still almost quadruple the national tuberculosis mortality rate.[8]

Morbidity Rates

With the gradual decline in mortality from most infectious diseases in the past five decades, mortality statistics are no longer satisfactory indices of disease endemicity; more reliance has to be placed on morbidity trends, especially when comparing morbidity statistics of one country with another. In international comparisons, the use of tuberculosis morbidity statistics is influenced by a multitude of factors: (1) the completeness of reporting, and whether it is mandatory; (2) the differences in the criteria that define a tuberculosis case (some countries report only bacteriologically-confirmed cases, while others report only respiratory tuberculosis); and (3) the availability of programs for organized case-finding.

WHO estimates of worldwide tuberculosis indicate that between 1990 and 1999, 88 million tuberculosis cases are expected to occur, of which eight million will be associated with HIV. During the same period, thirty million people are expected to die of tuberculosis, including 2.9 million attributable to HIV infection. The agency further predicts that the annual incidence of new cases will increase from the 7.5 million (143 per 100,000) in 1990 to 10.2 million (163 per 100,000) in 2000.[9]

In spite of the variability in reporting, surveillance, and case-finding, many countries in Africa, Asia, and South America are experiencing extremely high morbidity rates. In 1990, morbidity rates exceeding three hundred per 100,000 have been reported from Zambia and Boliva and exceeding two hundred per 100,000 from the Philippines, South Africa, Peru, Nigeria, and India. All evidence points to a devastating tuberculosis toll in most African countries.[10]

In Tanzania, five thousand more cases were reported in 1988 over the yearly average than during the preceding decade. In a rural Malawi hospital, for example, tuberculosis admissions increased by 160 percent between 1983 and 1988. Extrapulmonary tuberculosis was more frequently reported among younger patients. One study found that the prevalence of HIV infection in ambulatory patients with tuberculosis in Abidjan, Ivory Coast, increased from 25 percent in 1988 to 45 percent in 1990.[11]

Table 3 shows tuberculosis notification rates in selected European countries in 1975, 1980, 1985, and 1990. Generally speaking, a marked decline occurred in most countries

TABLE 3
Tuberculosis Notification Rates per 100,000 Population, 1975–1990

COUNTRY	1975	1980	1985	1990
Austria	32	29	19	20
Belgium	44	27	20	16
Finland	74	47	37	16
France	48	32	21	16
Germany	51	38	26	18
Ireland	37	34	23	18
Italy[1]	7	6	7	7
Netherlands	16	12	9	9
Portugal	100	70	68	60
Spain[2]	9	13	28	19
Sweden	18	11	8	7
Switzerland	33	18	15	18
United Kingdom	23	19	12	10

SOURCE: P. J. Dolin et al., "Global Tuberculosis Incidence and Mortality during 1990–2000," *Bulletin of the World Health Organization* 72 (1994): 213–20.

1. Bacteriologically confirmed cases.
2. Pulmonary tuberculosis only.

during that fifteen-year period (except in Spain), and the majority of cases occurred among the elderly. The exception was Portugal, where more than half occurred within the fifteen to forty-four age range.[12] Yearly morbidity rates showed a modest increase (ranging from 5 percent in Austria and the United Kingdom to 27 percent in Italy) among industrialized countries between the late 80s and early 90s.[13]

In developed countries, the traditional risk factors associated with tuberculosis morbidity and mortality still play an important role—poverty, overcrowding, homelessness, large household size, and ethnicity. Most cases are concentrated in large urban centers, where, in addition to the traditional environmental risk factors, there is a higher prevalence of HIV infections and a higher concentration of immigrants from developing countries.

Tuberculosis morbidity rates in the United States dropped from 46.9 per 100,000 in 1955 to 9.8 per 100,000 in 1993. Unfortunately, that drastic decline was not seen in large metropolitan areas; New York City had an incidence rate of 44.2 per 100,000 in 1993—a rate 450 percent higher than the national rate.[14]

The proportion of foreign-born tuberculosis cases in the United States reportedly rose from 21.6 percent in 1986 to 29.6 percent in 1993. Most of the foreign-born patients were from Latin America and Southeast Asia. The tuberculosis incidence rate among foreign-born immigrants measured within five years of their immigration almost quadrupled that of native residents.[15] The same phenomenon was observed in other industrialized countries. During 1990, 51 percent of all cases in Switzerland, 41 percent in the Netherlands, and 38 percent in Denmark occurred among foreign-born immigrants.[16]

Prevalence of Infection

In spite of the gradual decline in tuberculosis mortality and morbidity that occurred in many countries between 1950 and 1985, infection rates remained relatively high. The WHO estimated that in 1990 there were 1.7 billion people (or one third of the world population) infected with the tubercle bacillus. During the early 1950s, tuberculosis eradication was seriously considered as an attainable objective. The WHO Expert Committee set as its goal the control of the spread of infection to the extent that no more than

one percent of fourteen-year-old children in a country would react positively to a standard intermediate dose of tuberculin.[17]

A glance at the New York City tuberculin testing program among high school admissions aged thirteen to fifteen years during that period showed that the percentage of positive reactors to the Mantoux test varied from 10 percent in the 1959–1960 academic year, to 9.4 percent in 1960–1961 year, 12.5 percent in 1961–1962, and 17.1 percent in 1963–1964.[18] In California, positive reactor rates of 6 percent to 6.9 percent were reported between 1956 and 1959.[19] A long-term study of medical students in Chicago between 1939 and 1961 reported on the trend of tuberculous infection as indicated by reactions to low (two tuberculin units) and to high (100 tuberculin units) doses of tuberculin.[20] The study indicated that there had been a significant decrease in reactions to the low dose and a significant rise in high-dose reactions. The authors came to the conclusion that infection rates were still high despite declines in mortality and morbidity.

Thirty years later, infection rates continued to be high among minority groups, immigrants from highly endemic countries, persons with HIV infection, and other special groups. The changing epidemiology of tuberculosis in the last decade changed the interpretation of induration on the Mantoux test. An induration of five or more millimeters is now considered positive in those suspected of being HIV-positive, intravenous drug abusers, contacts of infectious cases, and those with radiographic abnormalities. An induration of ten or more millimeters is positive among persons born in highly endemic countries, health care workers exposed to high-risk individuals, children younger than four years, migrant workers, the homeless, and in the presence of other medical conditions. An induration of fifteen or more millimeters is positive among those with none of the risk factors mentioned previously.

The University of California at Los Angeles requires nonimmigrant foreign students to have a tuberculin test prior to registration. One study reported that of 589 students tested, 57.6 percent reacted positively to tuberculin (five millimeters of induration or greater).[21] Prevalence of infection was also studied in a random sample of farmworkers in North Carolina in 1991. Positive reactions there ranged from 33 percent in Hispanics, to 54 percent in American blacks, to 76 percent in Haitians.[22]

A study on prevalence of tuberculosis infection and prophylaxis among a sample of physicians at Barnes Hospital of St. Louis found that of the 351 physicians tested, nearly a quarter (eighty-six) were skin-test positive by history or by a currently performed skin test. Of forty physicians eligible for prophylaxis, only fifteen (37.5 percent) completed at least six months of therapy. Of 290 physicians previously negative, twenty-five (8.6 percent) tested positive. The authors concluded that tuberculous infection had become common among physicians.[23] Other studies among health care workers showed them to be at high risk of infection, especially if they were HIV positive.

Infection rates are staggeringly high in developing countries. A 1992 survey from Lima, Peru, found that of the 368 individuals tested, 34 percent had indurations of ten or more millimeters. Stratified by age, the results showed 12 percent positive reactors among children under two years of age, 18 percent for those between two and five, 60 percent for those between five and fifteen years, and 68 percent for those over twenty-

five years.Vaccination with Bacillus Calmette-Guerin (BCG) was responsible for the weak reactions.[24] A survey of 7,721 individuals from Saudi Arabia showed that 6 percent of the children five to fourteen years of age were positive reactors to the Mantoux test. Children living in urban areas had a higher positive reactor rate (10 percent) than those in rural areas (2 percent). The authors attributed the difference to the million pilgrims who every year visit urban areas.[25]

A survey in sub-Sahara Africa concluded that a majority of adults might be infected with *M. tuberculosis*. The annual tuberculin conversion rate (i.e., from negative to positive on the Mantoux test) in that region was estimated in the range of 1.5–2.5 percent. Moreover, there was a direct correlation between the annual infection rate and the annual incidence of sputum-smear positive tuberculosis.[26]

The Afghanistan Experience

During a sabbatical leave in 1971 and 1972, one of the authors, Mahfouz Zaki, was on assignment by the United States State Department as Peace Corps Physician and Advisor in Public Health to the Royal Government of Afghanistan (RGA). Apart from being responsible for the delivery of medical and preventive services to the volunteers and staff, one of his main charges was the promotion and initiation of public health programs in cooperation with the Afghan government. Of major public health concern were the extremely high birth rate and infant mortality rate. A family planning program incorporating maternal and child health was proposed to the RGA by Peace Corps/Afghanistan and the U.S. Agency for International Development. The program was accepted and was funded by Peace Corps/Washington.

The other outstanding problem was tuberculosis control. Despite the lack of vital statistics, rough estimates and special surveys demonstrated a strikingly high prevalence of tuberculous infection and disease in rural as well as urban populations. The tuberculosis problem and its extent and impact on the socioeconomic condition of the country had been recognized by Afghan public health authorities and the medical profession. Organized anti-tuberculosis activities had started only in 1954, however, with the establishment of the Tuberculosis Center in the capital, Kabul. In 1962 a plan of operation for tuberculosis advisory services was signed by the RGA and the WHO for the further development and expansion of tuberculosis control. As part of that plan a WHO medical officer was assigned and a limited direct BCG vaccination program was begun in the capital and in a few provinces.

Over a two-month period Zaki visited all the Afghan health centers involved in tuberculosis control. Organized community case-finding programs were practically nonexistent. Patients were usually discovered only after they had sought medical attention for prolonged respiratory symptoms. Diagnosis was made through smear examination and, on occasion, chest x-ray. Culture was infrequently resorted to in questionable cases and was performed only by the Institute of Public Health in Kabul, which acted also as a reference laboratory. The use of mass chest radiography, a productive case-finding tool in areas of high prevalence, was not well utilized because of the scarcity of x-ray machines and lack of film.

Tuberculin testing was not used for case-finding because in areas of such high prevalence the majority of the adult population

would have reacted positively to tuberculin and thus nullify its use for case-finding. Even at the family level in private practice, however, tuberculin testing was not usually performed. After diagnosis, patients were treated in municipal hospitals or by private practitioners on an ambulatory basis with isoniazid and thiacetazone. Therapy was usually for a short period, two to three months on the average; in only a few instances did the author find therapy continued for more than one year. Hospitalization was limited to patients with advanced disease or those with complications. Patients were usually encouraged, directly or indirectly, to continue with their therapy through private practitioners. Many patients did not have access to or could not afford private medical care, and their therapy was thus interrupted. Moreover, supplies and drugs were scarce, even in the municipal hospitals and health centers. During 1971 there were only 1,248 patients on the tuberculosis register in Kabul and the eleven provinces where control efforts were in operation. Considering the magnitude of the tuberculosis problem in Afghanistan, one could safely conclude that case-finding and chemotherapy were not employed to any meaningful extent.

Direct BCG vaccination (i.e., without prior tuberculin testing) was used for those under twenty years of age. The vaccine was mostly supplied by the United Nations Children's Fund. In many of the centers visited by the author, however, the vaccine was not available; and in most situations, coverage was incomplete. Chemoprophylaxis with isoniazid was rarely employed for the protection of household contacts or high-risk individuals.

In an attempt to obtain reliable estimates of the prevalence of tuberculosis and histoplasma infections and in response to a request from the RGA, Peace Corps/Afghanistan undertook an extensive prevalence survey in cooperation with the Centers for Disease Control and Prevention (CDC). The survey included all 1,030 incoming freshmen at Kabul University in the fall of 1971. Most of the students (93 percent) were males and most (96 percent) were between fifteen and twenty-four years of age. Each student was injected with four antigens supplied by the Tuberculosis Branch of the CDC. One antigen was from human strains of *M. tuberculosis* (five tuberculin units), one from an atypical strain (*Battey bacilli*), one from *Histoplasma capsulatum*, and one from *Candida albicans*. A double-blind approach was used. The antigens were color coded and were injected in doses of .10 ml by 26-gauge platinum needles in four sites in the two upper arms. Tests were read after seventy-two hours.

Conducting the prevalence survey was a fascinating experience. Following procurement of the antigens and other medical supplies from the CDC, the author was faced with a serious problem—the recruitment of staff to administer four intradermal antigens per person to more than 3,500 individuals (in addition to the university students, the survey included outpatients and elementary schoolchildren). The author and his wife (a registered nurse who volunteered to participate) were the only medical or nursing Peace Corps staff available. Fortunately, he was able to recruit the vacationing niece of an American Consortium surgeon at University Hospital, who also happened to be a registered nurse. One physician and two nurses could scarcely administer more than fourteen thousand intradermal injections, however, and so assistance was sought from nonmedical Peace Corps volunteers. Twelve

Table 4
Tuberculin Sensitivity Survey at Kabul University, Afghanistan, 1971

Age Group (years)	SIZE OF REACTION IN MILLIMETERS TO PPD-S						Total Tested & Read
	0–4		5–9		10+ millimeters		
	Number	Percent	Number	Percent	Number	Percent	
15–19	166	40.9	62	15.3	178	43.8	406
20–24	227	39.1	96	16.5	258	44.4	581
25–29	6	19.4	8	26.8	17	64.8	31
30+	3	25.0	1	8.3	8	66.7	12
TOTAL	402	39	167	16.2	461	44.8	1030
Male	363	38.4	148	15.6	435	46.0	946
Female	39	46.4	19	22.6	26	31.0	84

volunteers (architects and agriculture, music, and English majors) joined the survey team. Their crash course included an introduction to the antigens used, the reactions expected, and the intradermal procedures. It should be emphasized that the performance of the nonmedical volunteers in the administration of the Mantoux tests was excellent, as good as any well-trained medical or nursing staff.

The language barrier made it difficult to get accurate information relating to previous BCG vaccination. The question, therefore, was whether the student had had any previous immunization. (Preventive measures, including childhood immunizations, were hardly performed in Afghanistan.) BCG vaccination had been introduced around the Kabul area and in a few provinces, but the coverage was scattered. It was thus safely presumed that more than 90 percent of the students had not been vaccinated with BCG. The percentage of positive reactors among those with previous history of any immunization did not differ significantly from the same among those with no previous history of immunization.

About 34 percent of the students had reactions of four to nine millimeters to purified protein derivate B. Because of the lack of information on the prevalence of infection with atypical strains, a conservative position was adopted and a reaction of ten millimeters to purified protein derivate S was considered indicative of a past tuberculosis infection. As is evident from Table 4, of the 1,030 students tested, 39 percent had reactions of zero to four millimeters, 16.2 percent five to nine millimeters, and 44.8 percent 10 or more millimeters to five tuberculin units of *M. tuberculosis*.

The experience gleaned from the prevalence survey shows what can be accomplished by nonmedical staff in the areas of public health and preventive medicine. Indeed, it was to the credit of Peace Corps that both the Family Planning and Tuberculosis Control programs withstood all the political upheaval and fiscal crises and operated successfully until the U.S. government pulled out of Afghanistan in the late seventies. Had a similar prevalence survey been conducted in the United States, it would probably have cost more than $100,000, and would have

taken a couple of years to procure all the necessary administrative and legal approvals in order to avoid future litigation and malpractice suits.

Infection with MDR Strains

During the past four decades there has been growing concern over the prevalence of infections with drug-resistant strains of *M. tuberculosis* among previously untreated subjects, a phenomenon frequently referred to as "primary drug resistance." Although the exact nature of drug resistance and the intricate mechanism that leads to its development have not been fully elucidated, clinicians and public health physicians are acutely aware of the trend of infection with drug-resistant strains, the effect of drug-resistant strains on clinical progress of patients, and the transmission of infection among their contacts.

In this country and abroad, conflicting reports have been published on the prevalence and trend of infection with strains resistant to the first- and second-line drugs. In this paper, attention is given to selected studies only. One of the most important continuing surveys of drug resistance by the United States Public Health Service (USPHS) was done in cooperation with twenty-two state and city hospitals throughout the nation between 1961 and 1962. The survey demonstrated that out of 2,400 strains isolated, 1.6 percent were resistant to isoniazid (INH), 2.8 percent were resistant to streptomycin (SM), and 0.8 percent were resistant to para-aminosalicylic acid (PAS).[27]

In a five-year study of drug resistance of 1,777 isolates in New York City, researchers using the USPHS cooperative study criteria found that the rate of infection with strains resistant to INH increased from 11.5 percent of all infections in 1960 to 23.2 percent in 1964. The increase was attributable to strains resistant to INH alone—6.5 percent in 1960 and 17.3 percent in 1964.[28]

A recent study compared drug-resistance patterns in the United States by geographic distribution, demographic characteristics, and risk factors. The patient population studied consisted of all patients with positive cultures reported in the first quarter of 1991. Resistance to one or more drugs was found in 14.2 percent of cases; resistance to INH and/or rifampin was found in 9.5 percent of cases whose isolates were tested against one or both drugs. Those cases were reported from thirty-three states. Resistance to both INH and rifampin was 3.5 percent of cases reported from thirteen states. The authors also found that MDR-TB in New York City was 52.4 times that of the rest of the nation. The relative risk among whites in New York City was 39.0 that of non-Hispanic whites in the rest of the nation, 299.3 of Hispanics, 420.9 of Asian/Pacific Islanders, and 701.0 of non-Hispanic blacks.[29]

Another study described the incidence of MDR-TB among residents of the tuberculosis unit of the New York municipal shelter system. Among fifty-eight isolates of *M. tuberculosis*, eight were resistant to one drug (14 percent) and an additional nine were resistant to at least two drugs (16 percent). A history of previous treatment among homeless men was associated with increased risk of having MDR.[30]

In a study of 1,181 bacteriologically-positive cases reported between 1983 and 1992 in Israel, researchers found that 12.6 percent of isolates were resistant to one drug (7.3 percent) or more than one drug (5.3 percent).[31] The highest incidence of drug-resistant bacilli was among immigrants from the Soviet Union (37.3 percent) and Ethiopia (16.2 percent). In a 1995 study of 2,509 Aus-

American nurses Nina Zeller (at left) and Kathryn Zaki administer skin tests in Kabul, Afghanistan, in 1971.

tralian residents with bacteriologically-confirmed tuberculosis, resistance to at least one of the common antituberculosis drugs was detected in 14.4 percent of isolates; resistance usually involved INH (8.4 percent) and SM (7.6 percent). Fewer than one percent were resistant to both INH and rifampin.[32]

A report published in 1993 from England and Wales showed that between 1982 and 1991, over sixteen thousand isolates had resistant strains.[33] The proportion of initial isolates resistant to one or more drugs ranged from 8–10.9 percent between 1982 and 1990. In 1991, however, that increased to 14.2 percent. MDR, however, remained low.

The advent of effective antibiotics and chemotherapeutics in the 1950s and 1960s had two unfortunate consequences: infection control practices in hospitals were relaxed, and nosocomial infections increased. By the late 1980s, the upsurge of tuberculosis and MDR strains were subjecting health care workers—especially those involved in cough-producing procedures—to a higher risk of infection. One study not only documented outbreaks of MDR strains in twelve hospitals but also found conversion rates ranging from 18–35 percent among exposed health care workers.[34]

To combat the high concentrations of MDR strains, tuberculosis, and HIV infections in large urban areas, the CDC developed a National Action Plan. The plan calls for: (1) greater surveillance and epidemiologic studies of MDR-TB; (2) initiatives to improve the rapidity, sensitivity, and reliability of diagnostic methods for MDR-TB; (3) programs to ensure the regularity and effectiveness of therapeutic regimens; (4) preventing those infected with susceptible strains from developing drug resistance; (5) screening

programs for identifying those at risk of developing MDR-TB and preventing them from developing active disease; (6) expansion of infection control programs to reduce nosocomial infections; (7) training and education of health care workers regarding MDR-TB epidemiology and prevention; (8) outbreak control; and (9) program evaluation.[35]

The multitude of factors that play a role in drug resistance, whether primary or acquired, make comparative studies an extremely difficult task. That is especially true today because of the lack of agreement on the criteria for significant drug resistance as well as on the most efficient or appropriate techniques for testing drug sensitivity. Whatever the absolute figures are, the most important fact is that there is a definite increase in infections with strains resistant to first-line drugs.

More extensive epidemiologic, laboratory, and clinical studies are surely needed. Such studies should include transmission of drug-resistant strains, testing techniques, criteria of resistance, and the relationship of *in vitro* resistance to *in vivo* response. It may also be important for the major chest disease services to initiate and encourage "resistance surveillance units" using uniform techniques and criteria to help demonstrate the prevalence of resistant strains.

Regularity of Drug Administration

The development of potent chemotherapeutics for the treatment of tuberculosis, plus the skyrocketing cost of hospitalization during the 1950s and 1960s, caused a shift in the locale of therapy from the hospital or sanatorium to the patient's home. That trend was given further impetus by the well-publicized success of ambulatory programs conducted by Wallace Fox in Madras, India, in the late 1950s, which were supported by the British Medical Research Council.[36]

With the adoption of domiciliary treatment, the question of regularity of drug administration was often raised. The regimen of choice for such treatment was one or two years of therapy with SM, INH, and PAS. Studies conducted in this country and abroad showed that hospitalized patients took their medication more regularly than those under domiciliary treatment.

In a study of the regularity of drug administration by Zaki and others, tuberculosis patients hospitalized at Kings County Hospital Center, Brooklyn, were matched with an equal number of comparable patients treated on an ambulatory basis by the health department chest disease clinics. All patients were being treated with INH and PAS. Surprise visits were made to obtain urine samples from both groups in order to determine whether they differed significantly in the regularity of INH and PAS administration. Researchers found that 96 percent of the hospitalized patients were taking both drugs on the day of examination, whereas only 56 percent of the ambulatory patients were taking INH and 52 percent of them were taking PAS.[37] A similar study reported that 90 percent of hospitalized patients took PAS regularly, compared with only 35.5 percent of ambulatory patients. Neves Almeida reported from Portugal that 70 percent of 1,306 inpatients and 47 percent of 469 outpatients had urine-positive results for PAS.[38]

All of those studies pointed to the inadequacies of ambulatory treatment of tuberculosis patients, which resulted in the development of MDR and a high relapse rate. The authors also advocated either an initial hospitalization period to train or condition the patient to follow the necessary

regimen or upgrade and closely supervise drug administration in the ambulatory setting. The practice of directly observed therapy (DOT) was introduced in the 1980s and recommended as an integral part of a tuberculosis control program. The comparison of incidence of drug resistance and relapse among tuberculosis patients in Tarrant County, Texas, prior to and after the institution of DOT was encouraging. Between January 1980 and October 1986, 407 patients with positive cultures received traditional treatment; between 1986 and 1992, 581 patients received medication under DOT. The authors noted that despite the higher rate of intravenous drug use and homelessness during the thirteen-year study period, the frequency of primary drug resistance decreased from 13 percent to 6.7 percent after the institution of DOT, and the frequency of acquired drug resistance declined from 14 percent to 2.1 percent. The number of relapses with MDR organisms decreased from twenty-five to five. The authors concluded that DOT significantly reduced both the relapse rate and the frequency of primary and acquired drug resistance.[39]

Currently recommended therapy for patients infected with susceptible strains consists of INH, rifampin, and pyrazinamide for two months, followed by INH and rifampin for four months. Ethambutol or SM should be included in the initial treatment pending sensitivity studies. Such four-drug therapy over a six-month period is effective even if the infecting strain is resistant to INH. Treatment of MDR infections, however, must be individualized. If the strain is resistant to first-line drugs, second-line drugs may have to be used and treatment may be extended to twenty-four months. Caution should be taken to monitor side reactions since most second-line drugs are not as well tolerated as first-line drugs. Today more than ever, the emergence of MDR strains and the standard short-term therapies mandate the deployment of DOT.

Co-Infection with HIV

The incidence of tuberculosis is substantially increased in HIV-infected individuals. As a matter of fact, the TB/HIV co-infection is the fastest-growing epidemic. It has been estimated that tuberculosis occurs five hundred times more frequently in HIV-infected individuals than in the general population.[40] The WHO estimated that approximately four million people had been infected with both the *M. tuberculosis* and HIV since the beginning of the pandemic. Of those, 95 percent were in developing countries.[41] The impact on Africa and Asia has been devastating. Since the 1980s, the annual number of TB cases with HIV co-infection has nearly tripled in Zambia and more than doubled in Malawi.[42] In 1990 co-infection represented 4.2 percent of all tuberculosis cases, and predictions are that it would account for 8.4 percent in 1995 and 13.4 by the year 2000.[43]

Surveillance data reported to the CDC during 1981–1994 indicated that among 441,528 persons reported to have AIDS, 20,136 (4.6 percent) had extrapulmonary tuberculosis and 6,432 (1.4 percent) had pulmonary tuberculosis.44 A United States study of AIDS/TB dual infections from 1981 through 1991 concluded that "the risk of TB or AIDS among persons diagnosed with one disease is much higher than the general population." The authors further estimated that the immunosuppression caused by the HIV infection might have accounted for at least 30 percent of new TB cases between 1985 and 1990.[45] A study of INH prophylaxis on the incidence of active tuberculosis and

the progression of HIV infection in Port-au-Prince, Haiti, reported that the drug effectively decreased the incidence of tuberculosis and delayed the onset of HIV-related disease in symptom-free HIV-seropositive individuals.[46] INH was also shown to be an effective prophylactic for HIV-infected tuberculin reactors and for many HIV-infected anergic patients.[47]

Although primary tuberculosis has occurred occasionally in HIV-infected individuals, the majority of clinical tuberculosis in that population is due to a reactivation of a latent infection. That underscores the need for tuberculin testing of drug injectors with known or suspected HIV infection and the administration of INH prophylaxis for both the anergic and tuberculin-positive reactors. TB/HIV infections changed the tuberculosis mortality pattern dramatically. Prior to the AIDS era, the tuberculosis mortality peak was among the elderly. Now, another peak has emerged among patients twenty to forty-nine years of age, resulting in a bimodal mortality curve. The co-infection dilemma has been further compounded by the frequent infection with MDR strains and the occurrence of epidemics.

Prospects for Eradication

Experience with tuberculosis has demonstrated that effective control cannot be achieved simply by the development of chemotherapeutic drugs or attempts at early case-finding. An illustration is the story of sexually-transmitted diseases. Following the introduction of penicillin with its dramatic effect on gonorrhea and syphilis over fifty years ago, elimination of at least those two diseases was considered to be a one-decade operation. Instead, more than 500,000 cases are yearly reported to the CDC, a figure that is probably only half or even a third of the total number of cases. The upsurge of primary and secondary syphilis between 1988 and 1992 in large metropolitan areas in this country demonstrates the difficulties encountered in the elimination process.

Believers in the "No Tuberculosis by 1960" slogan were confident that the marked decline in tuberculosis mortality and the relative decline in morbidity would result in eradication, and their predictions were substantiated by various mathematical models. Many of those models were based on very rough estimates of infection and relapse rates, however, and on the results of early chemoprophylactic trials. Incidence rates were projected as a function of large-scale application of various control measures, including effective chemoprophylaxis of all infected individuals or even mass BCG vaccination of children. Considering the many determinants that are incorporated in tuberculosis epidemiology and the difficulty that may be encountered in enforcing control measures of that nature on a mass basis, one would be inclined to question the validity of such models. Today the tuberculosis situation in Africa, Asia, Central America, South America, and some urban centers in developed countries is far from encouraging; infection rates in the child population may reach as high as 30 or 40 percent. Talk of eradication in those countries seems quite premature.

Funding for tuberculosis programs during the 1960s and 1970s was handicapped by misleading inferences concerning the resolution of the tuberculosis problem. Whether in this country or worldwide, funding dwindled to an embarrassing level. Of the $811 million in foreign aid to the WHO in 1990, only $16 million was allocated for tuberculosis, the least amount spent on an infectious

disease.[48] The decline of appropriations for tuberculosis control by the United States government and the State of New York over the past fifteen years are shown in Table 5.[49] It is difficult to believe that the richest and most technologically advanced country in the world would appropriate $3.6 million for tuberculosis control in 1980 for a population of more than 230 million.

Relaxation of control measures and reduction of funding for a declining disease are among the most common errors in preventive medicine and public health policy decision-making. It is at that stage of decline when all available tools should not only be deployed but augmented. A swift massive assault could thus be directed toward the remaining pockets of infection, leading to the eventual elimination of the disease. The cost of the resurgence of tuberculosis has been astronomical. For illustration, between 1979 and 1994 approximately twenty thousand new tuberculosis cases occurred in New York City. Those cases would not have occurred had the previous declining trend continued. The total cost of care for those patients exceeded $400 million.[50] In addition, the cost of hospitalizing about one third of those patients (in addition to expenditures for hospital renovations and prophylactic therapy) pushed the final cost in excess of one billion dollars.

Serious funding should be allocated for the following objectives:

- Search for new chemotherapeutics for the treatment of MDR-TB (existing treatment regimens require the administration of four to six agents that are not always well tolerated).
- Establish DOT as the standard of care, especially for MDR strains.

Table 5
Federal and New York State Tuberculosis Control Appropriations

YEAR	UNITED STATES		STATE OF NEW YORK	
	Incidence	Funding	Incidence	Funding
1980	27,769	$ 3,600,000	2,294	$ 4,377,600
1985	22,201	9,250,000	2,481	514,304
1990	25,701	22,533,000	4,176	1,738,450
1991	26,283	25,274,000	4,421	2,855,000
1992	26,673	46,486,000	4,574	8,739,053
1993	25,287	104,298,000	3,952	29,573,466
1994	24,361	142,232,000	3,636	31,497,467
1995		145,045,000		32,690,822

- Initiate screening programs, especially for high-risk individuals and those older than fifty years of age.
- Conduct proper case management to ensure that patients follow their therapeutic regimens.
- Initiate tuberculosis infection control measures for health care facilities.
- Begin selective BCG vaccination programs.

Winning the fight against disease is analogous to winning a war, and no one could explain that concept more eloquently than General Douglas MacArthur in his address to the joint session of Congress on April 19, 1951:

> [O]nce war is forced upon us, there is no other alternative than to apply every available means to bring it to a swift end. War's very object is victory—not prolonged indecision. In war, indeed there can be no substitute for victory.
>
> For history teaches us with unmistakable emphasis that appeasement but begets new and bloodier war. It points to no single instance where the end has justified that means—where appeasement has led to more than sham peace. Like blackmail, it lays the basis for new and successively greater demands,

until as in blackmail, violence becomes the only other alternative.[51]

Unfortunately, tuberculosis had lost its constituency and intrigue by the 1970s. Elected officials and budget officers used the declining morbidity and mortality to reduce appropriations for tuberculosis control. Those reductions resulted in the weakening of already-mediocre programs in case-finding, supervision of drug administration, prophylaxis, and follow-up. MDR strains emerged, combining with HIV to cause an upsurge of tuberculosis as a major public health problem.

The current tuberculosis crisis is totally different from the earlier tuberculosis scenario. Previously, most mycobacterial strains were susceptible to first-line drugs, there was no concomitant HIV infections, and specialized hospitals or sanatoria offered supervised therapy. Today, many tuberculosis patients are infected with MDR strains, have concomitant HIV infection, and are treated at home; some are poverty stricken or homeless and have no access to appropriate medical care.

Many factors, both epidemiological and social, will impede the elimination process: the pathological nature of tuberculosis; its chronicity; the ability of the tubercle bacillus to remain alive in the human body for years; the changing patterns of morbidity and mortality among age groups; increased life expectancy; the high prevalence of active disease and infection rate in developing countries and in select groups in developed countries; the alarming increase in MDR strains; the concomitant infection with HIV; the relatively high reactivation rate; and the changing epidemiology of tuberculosis, including the recent occurrence of epidemics.[52]

The past two decades have witnessed a dramatic emphasis on environmental contaminants and their impact on human health. The wide publicity given incidents such as the Love Canal in New York State and the possible deleterious effects of exposure to Agent Orange have heightened public awareness and, in a sense, engendered a state of environmental paranoia. Our society seems to be willing to accept tangible and measurable risks resulting from such infections as *M. tuberculosis*, cigarette-smoking, and excessive alcohol intake. The same society, however, is unable to tolerate potential, intangible, and unmeasurable risks from food additives, pesticides, air pollutants, and water contaminants. The fascination with environmental contaminants by politicians and the public at large has resulted in the misappropriation of billions of dollars for the environment at the expense of such basic intrinsic needs as tuberculosis control.

The failure of this country to contain the tuberculosis problem is unfortunate, shortsighted, and disgraceful. The United States should set an example for the whole world—not only by embarking on an all-out offensive against the tuberculosis problem in this country but also by providing substantial funding to the WHO for combating the disease worldwide. It cannot be overemphasized that a sizeable proportion of tuberculosis patients in developed countries are immigrants from highly endemic areas. In other words, our assistance to the international effort will eventually benefit the United States.

♦

Notes

1. L. I. Dublin, "No More Tuberculosis by 1960," *Survey Graphics* 46 (1941): 33–36.

2. J. A. Perkins, "Global Tuberculosis Eradication," *American Review of Respiratory Disease* 80 (1959): 138–39.

3. The Arden House Conference on Tuberculosis, Harriman, N.Y., United States Public Health Service, Department of Health, Education and Welfare, 1959.

4. F. L. Soper, "Problems to Be Solved if the Eradication of Tuberculosis Is to Be Realized," *American Journal of Public Health* 52 (1962): 724–45.

5. Centers for Disease Control and Prevention, "Estimates of Future Global Tuberculosis Morbidity and Mortality," *Morbidity and Mortality Weekly Report* 42 (1993): 961–64.

6. Ibid.

7. M. M. Braun, T. R. Cote, and C. S. Rabkin, "Trends in Death with Tuberculosis during the AIDS Era," *JAMA* 269 (1993): 2865–68.

8. Centers for Disease Control and Prevention, USPHS, personal communication to the authors, 1995; Bureau of Tuberculosis Control, Department of Health, City of New York, personal communication to the authors, 1995.

9. P. J. Dolin, M. C. Raviglione, and A. Kochi, "Global Tuberculosis Incidence and Mortality during 1990–2000," *Bulletin of the World Health Organization* 72 (1994): 213–20.

10. World Health Organization, *Report on the TB Epidemic: TB, A Global Emergency* (Geneva:WHO, 1994).

11. K. M. DeCock et al., "Tuberculosis and HIV Infection in Sub-Saharan Africa," *JAMA* 268 (1992): 1581–87.

12. Dolin et al., "Global Tuberculosis Incidence."

13. World Health Organization, *Report on the TB Epidemic.*

14. Bureau of Tuberculosis Control, Department of Health, City of New York, personal communication to the authors, 1995.

15. M. T. McKenna, E. McGray, and I. Bronato, "The Epidemiology of Tuberculosis among Foreign-born Persons in the United States, 1986–1993," *New England Journal of Medicine* 33 (1995): 229–33.

16. Dolin et al., "Global Tuberculosis Incidence."

17. A. Kochi, "Government Intervention Programs in HIV/Tuberculous Infection," *Bulletin of the International Union against Tuberculosis and Lung Disease* 66 (1991): 33–36.

18. R. S. Merchant, *Tuberculosis in New York City* (New York: Tuberculosis and Health Association, 1964).

19. F. J. Curry, "Tuberculin Skin Testing in San Francisco Schools," *American Journal of Public Health* 52 (1962): 616–26.

20. S. R. Rosenthal, M. J. Colbert, and I. Nikurs, "Tuberculin Reaction Trend and BCG Vaccination," *Archives of Environmental Health* 11 (1965): 794–803.

21. S. Quillan, C. K. Malotte, and D. Shlian, "Evaluation of a Tuberculosis Screening and Prophylaxis Program for International Students," *Journal of American College Health* 38 (1990): 165–70.

22. S. D. Ciesielski et al., "The Epidemiology of Tuberculosis among North Carolina Migrant Farm Workers," *JAMA* 265 (1991): 1715–19.

23. V. J. Fraser et al., "Screening of Physicians for Tuberculosis," *Infection Control and Hospital Epidemiology* 15 (1994): 95–100.

24. W. S. Getchell et al., "Basic Epidemiology of Tuberculosis in Peru: A Prevalence Study of Tuberculin Sensitivity in Pueblo Joven," *American Journal of Tropical Medicine and Hygiene* 47 (1992): 721–29.

25. F. A. Kassimi et al., "Nationwide Community Survey of Tuberculosis Epidemiology in Saudi Arabia," *Tubercle and Lung Disease* 74 (1993): 254–60.

26. DeCock et al., "Tuberculosis and HIV Infection."

27. U.S. Public Health Service, "Cooperative Investigation: Prevalence of Drug Resistance in Previously Untreated Patients," *American Review of Respiratory Disease* 89 (1964): 327–36.

28. M. H. Zaki et al., "The Trend of Infection with Drug-resistant Strains of Mycobacterium Tuberculosis among Untreated Patients," *American Journal of Public Health* 59 (1969): 2056–66.

29. A. B. Bloch et al., "Nationwide Survey of Drug-resistant Tuberculosis in the United States," *JAMA* 271 (1994): 665–71.

30. J. Concato and W. N. Rom, "Endemic Tuberculosis among Homeless Men in New York City," *Archives of Internal Medicine* 154 (1994): 2069–73.

31. A. Lavy and A. Mates, "A 10-year Survey and Mycobacterium Tuberculosis in Israel and Their Drug Resistance," *Israel Journal of Medical Science* 30 (1994): 805–10.

32. D. J. Dawson et al., "Tuberculosis in Australia, 1980–1992: Bacteriologically Confirmed Cases and Drug Resistance," *Medical Journal of Australia* 162 (1995): 287–90.

33. A. R. Warburton et al., "Drug Resistance in Initial Isolates of Mycobacterium Tuberculosis in England and Wales, 1982–1991," *Communicable Disease Report* 3 (1993): 175–79.

34. D. Menzies et al., "Tuberculosis among Health Care Workers," *New England Journal of Medicine* 332 (1995): 92–98.

35. Centers for Disease Control and Prevention, USPHS, "National Action Plan to Combat Multidrug-resistant Tuberculosis," *Morbidity and Mortality Weekly Report* 41 (1992): 5–48.

36. W. Fox, "The Chemotherapy and Epidemiology of Tuberculosis," *Lancet* 2 (1962): 413–17.

37. M. H. Zaki, S. Edelstein, R. A. Josephson, and S. R. Weisberg, "Regularity of Drug Administration among Hospitalized and Ambulatory Tuberculous

Patients," *American Review of Respiratory Disease* 97 (1968): 136–39.

38. Ibid.

39. S. E. Weis et al., "The Effect of Directly Observed Therapy on the Rates of Drug Resistance and Relapse in Tuberculosis," *New England Journal of Medicine* 330 (1994): 1179–84.

40. P. F. Barnes et al., "Tuberculosis in Patients with Human Immunodeficiency Virus Infection," *New England Journal of Medicine* 324 (1991): 1644–50.

41. J. P. Narain, M. C. Raviglione, and A. Kochi, "HIV Associated Tuberculosis in Developing Countries: Epidemiology and Strategies for Prevention," *Tubercle and Lung Disease* 73 (1992): 311–21.

42. World Health Organization, *Report on the TB Epidemic.*

43. P. J. Dolin, M. C. Raviglione, and A. Kochi, "Estimates of Future Global Tuberculosis Morbidity and Mortality," *JAMA* 271 (1994): 739–41.

44. Centers for Disease Control and Prevention Reports.

45. D. R. Burwen et al., "National Trends in the Occurrence of Tuberculosis and Acquired Immunodeficiency Syndrome," *Archives of Internal Medicine* 155 (1995): 1281–86.

46. J. W. Pape et al., "Effect of Isoniazid Prophylaxis on Incidence of Active Tuberculosis and Progression of HIV Infection," *Lancet* 342 (1993): 268–72.

47. D. N. Rose, C. B. Schechter, and H. S. Sacks, "Preventive Medicine for HIV-infected Patients: An Analysis of Isoniazid Prophylaxis for Tuberculosis Reactors and for Anergic Patients," *Journal of General Internal Medicine* 7 (1992): 589–94.

48. World Health Organization, *Report on the TB Epidemic.*

49. Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, personal communication to authors, 1995.

50. T. R. Frieden et al., "Tuberculosis in New York City: Turning the Tide," *New England Journal of Medicine* 333 (1995): 229–33.

51. D. Clayton James, *The Years of MacArthur: Triumph and Disaster 1945–1965* (Boston: Houghton Mifflin Company, 1985).

52. M. H. Zaki, "On the Epidemiology of Tuberculosis in Some Selected Countries: Highlights and Prospects for Control and Eradication, Part 11," *American Journal of Public Health* 61 (1971): 843–54.

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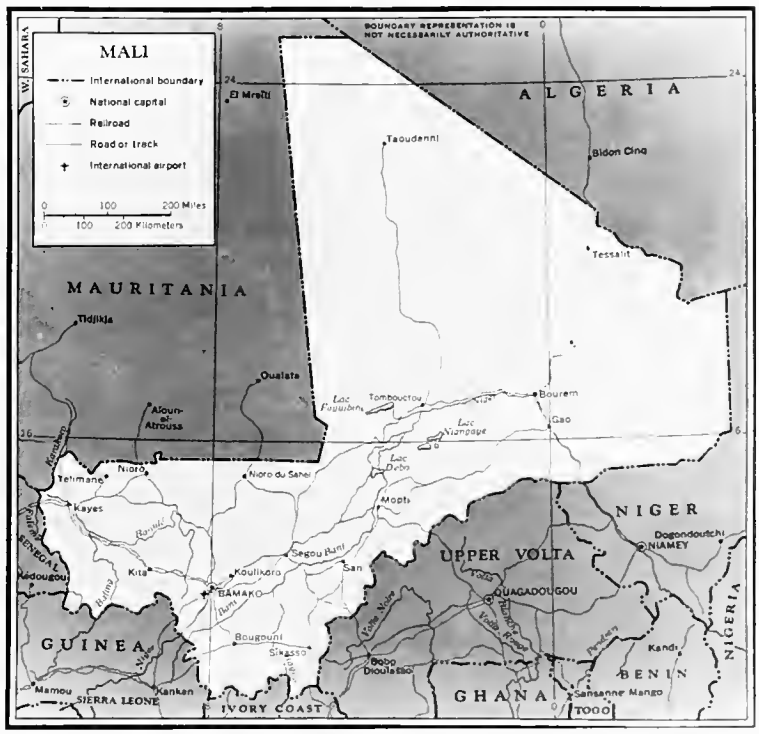
Smallpox and Measles in Mali: Contrasting Control Strategies and Outcomes

Pascal James Imperato

The last naturally transmitted case of human smallpox occurred in October 1977 in Merca, Somalia. In May 1980, the Thirty-third World Health Assembly accepted the report of the Global Commission for the Certification of Smallpox Eradication, which affirmed that the disease was eradicated.[1]

The intensive worldwide effort to eradicate smallpox began in 1966 when the Nineteenth World Health Assembly established an Intensified Smallpox Eradication Program and provided it with a budget of $2.4 million.[2] What made the objective of eradication possible were several technological advances, including automatic jet injectors, bifurcated needles capable of swift and safe vaccine delivery, and the development of heat-stable, freeze-dried smallpox vaccines. Equally important was the steady development of a commitment to eradicate smallpox. Developing a consensus around that objective was greatly facilitated through the leadership of the World Health Organization (WHO).

In the United States, the Centers for Disease Control (CDC), an agency of the U.S. Public Health Service, developed significant expertise in smallpox control during the 1950s and early 1960s. The name of this agency has been changed several times. It was originally known as the Communicable Disease Center, and later as the National Communicable Disease Center, the Center for Disease Control, the Centers for Disease Control, and finally as the Centers for Disease



The Republic of Mali (courtesy U.S. Department of State)

Late eruptive stage of smallpox in a young boy, Koutiala, Mali, 1967

Control and Prevention. In 1962 the CDC established a Smallpox Surveillance Unit under the direction of Dr. J. Donald Millar, who had had experience with the disease in Indonesia. Millar's unit was part of the CDC Surveillance Section, then headed by Dr. Donald A. Henderson, who would later become Chief of the WHO Smallpox Eradication Unit.

By early 1965, the CDC had clearly demonstrated in Brazil that a recently developed foot-powered jet injector could rapidly vaccinate large numbers of people against smallpox. That important technological advance, coupled with the availability of freeze-dried vaccines, put eradication within reach. Although WHO had a firm commitment to smallpox eradication, public health officials in West Africa were more concerned with measles, which had a higher mortality rate than smallpox. There, smallpox was a relatively mild disease.

During 1962 and 1963, Dr. Paul Lambin, Minister of Health of Upper Volta (now Burkina Faso), and Dr. Harry Meyer of the U.S. Division of Biological Standards organized the vaccination of some 700,000 children against measles in that country. The dramatic decline in measles incidence following that campaign created a demand by other West African countries for similar programs. The request found a positive response within the U.S. Agency for International Development (USAID), the branch of the State Department responsible for foreign assistance. To some degree, the positive response by USAID was shaped by the Cold War political environment, which significantly influenced United States foreign assistance programs, especially in newly independent African nations.

Former French colonies in West Africa were and still are joined in a regional communicable disease control organization known as the Organisation de Coordination et de Coopération pour la Lutte Contre les Grandes Endemies (OCCGE). A similar organization existed for former French colonies in Central Africa. Within the context of these regional groupings, the governments of African countries were able to make a concerted appeal for help with measles control.

The CDC interest in smallpox eradication and the USAID commitment to help with measles control represented potentially divergent public health objectives. Bringing them together in a unified American foreign assistance program required much negotiating effort on the part of both the CDC and USAID as described in great detail by Hor-

ace Ogden.[3] Unifying the programs in the field in French-speaking West African countries was relatively easy since each had multipurpose mobile health teams that were part of endemic disease services.

In late 1966 and early 1967, the CDC and USAID jointly set up a smallpox eradication/measles control program in nineteen West and Central African countries. The United States government pledged some $33 million for the effort.[4] To implement the program, the CDC hired and trained medical officers and operations officers, most of whom were in place in Africa by early 1967.

Early eruptive stage of smallpox in a young boy, Ansongo, Mali, 1967

The Republic of Mali

Mali is a landlocked country in the semiarid interior of West Africa. It covers 478,767 square miles and shares borders with seven countries. Formerly known as the French Sudan, Mali became independent in 1960 under a Marxist government that then maintained close bilateral ties with China, the Soviet Union, and the Eastern Bloc.

At the inception of Mali's smallpox eradication/measles control program in late 1966, the country had a population of four million. Approximately 90 percent lived in rural areas as either subsistence farmers or nomadic herdsmen. Because of its location, Mali has been subjected to cyclical droughts. In most years, however, the country is self-sufficient in food production. The major exports are cattle and hides, fish, and cotton.

The population of Mali has since more than doubled to nine million. The rural population of Mali is comprised of several different ethnic groups, only some of whom share linguistic and cultural characteristics. Approximately 65 percent of the population is Moslem, and the remainder follow various indigenous religions.[5]

Mali's Health Services in the 1960s and 1970s

Health services in Mali were first established in the 1890s, primarily by French military physicians. As the colonial government expanded, these physicians also provided services to the indigenous population. It was apparent to medical officers that health services had to become mobile and had to stress disease prevention if they were to have an appreciable impact on the health of the population. For that reason, and to deal with trypanosomiasis, a mobile medical service was established in French West Africa in 1939. In Mali, the service was called the Service National des Grandes Endemies (Endemic Disease Service), which conducted mass immunization programs and also provided diagnosis and treatment for leprosy, trypanosomiasis, malaria, trachoma, tuberculosis, and other communicable diseases.

Author removing smallpox scabs for laboratory testing, Lellehoi, Mali, 1967. The child being held on the left is in the early stage of the disease.

Health services were quickly Africanized in Mali in 1960 at independence, in contrast to some neighboring states that maintained closer ties with France. During the 1960s, large numbers of medical and paramedical personnel came from the Soviet Union, North Vietnam, and the People's Republic of China. Malians were sent to study medicine in the Soviet Union, Poland, and the German Democratic Republic. Most Malians who went to study medicine in France (about one hundred persons), however, did not return.

The colonial government also established the Assistance Médicale, the curative-care system, which was greatly expanded after independence. The medical care infrastructure for the 1970s included two national hospitals (Point-G and Gabriel Touré), a regional ophthalmologic hospital administered by the Organisation de Coordination et de Coopération pour la Lutte Contre les Grandes Endemies (OCCGE) and nine regional- and cercle-level (district) hospitals. In principle, each of the forty-six cercles and 281 arrondissements (ward subdivisions) was intended to have health centers, although in 1966 most arrondissements did not. In the 1960s and 1970s, more than half of the health personnel—as well as most of the drugs and supplies—were in the capital, Bamako, and served only 8 percent of the total national population. The Ministry of Health budget then ranged from 4 to 8 percent of the national budget; most health facilities were operated by the government and most personnel were government employees. In general, facilities were poorly maintained, suffered numerous equipment breakdowns, and—unless supported by outside donor projects—frequently lacked basic supplies and medications. Personnel costs were met by decreasing funds allocated for drugs and supplies. Thus, many facilities were only marginally functional.[6]

At the inception of the Mali smallpox eradication/measles control program in late 1966, most mobile teams of the Endemic Disease Service had not been functioning for a few years because of a lack of vehicles, spare parts, and funds for fuel. Some of the older personnel were extremely experienced in the delivery of mobile health services, however. In anticipation of the inception of the

USAID program, the government hired a score of young men in 1966 to be trained as vaccinators. Most were teenagers who had been eliminated from continuing their secondary education through competitive examinations.

The Smallpox Eradication/Measles Control Program in Mali

The smallpox eradication/measles control program for Mali was funded at a level of $1.2 million for a five-year period. That amount covered twenty Dodge trucks and spare parts, equipment, vaccines, and the personnel costs of a medical and operations officer. Jay Friedman and Mark D. Lapointe successively served as operations officers between 1966 and 1971. The program was administratively linked to the Endemic Disease Service. Because that agency was without a director from 1966 through 1968, the USAID personnel related directly to the Malian Director General of Health.

USAID advisors assisted the Malian Ministry of Health in establishing a comprehensive smallpox eradication/measles control program, set targets for it, and helped improve the disease surveillance system so as to permit the early detection of smallpox cases. The American advisors also were responsible for the training of Malian personnel, which included training in the handling of vaccines, use and repair of the Ped-O-Jet automatic jet injectors, organization and administration of vaccination sessions, maintenance and repair of the trucks, disease surveillance, and recordkeeping.

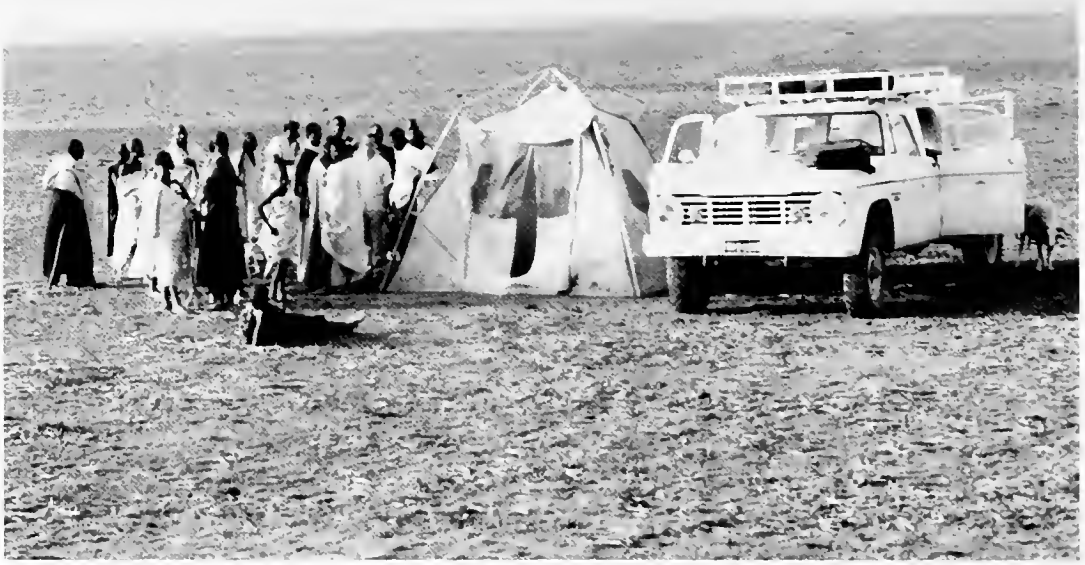
Obstacles to the Success of the Program

USAID personnel confronted several serious problems. The Marxist political climate of Mali became increasingly radicalized in 1967 with the launching of a cultural revolution by then-President Modibo Keita. Official anti-American sentiment was extremely strong, regularly expressed over the national radio and in the government-run newspaper. That sentiment was fueled by the Vietnam War and Mali's strong support of North Vietnam. Mali was a highly controlled Marxist state in which westerners, and especially Americans, were viewed with suspicion. The active harassment of the American diplomatic community was encouraged by the government. Not surprisingly, the American staff often found it difficult to secure cooperation from Malian health officials.

A smallpox eradication program had been started in Mali in 1962. Using two mobile teams and fifteen persons, it administered both freeze-dried vaccine produced in the Soviet Union and yellow fever vaccine made in Senegal. From the outset, the program had been handicapped by the lack of trained personnel, vehicles, and fuel. In addition, the absence of functioning refrigerators resulted in vaccine being stored at high ambient temperatures. As a result, heat-induced vaccine deterioration resulted in low "take" rates among those vaccinated.

Another problem was that people were not vaccinated in their villages but called to assembly points several miles away. As a result, there was selective vaccination of specific age groups. Children too big to be carried and too small to walk were left unvaccinated, as were the elderly and those occupied with agricultural labor.

Despite the administration of almost two million doses of smallpox vaccine between 1962 and 1966, cases of smallpox continued to occur in Mali. However, the annual number of reported cases declined to 281 in 1966. A WHO team assessing the Malian program in 1965 described the prospects of eradication as "bleak." The report estimated that it



Author holding a vaccination session for Peul nomads near Lake Debo in the Inland Delta of the Niger, Mali, 1968

would take a decade to eradicate the disease.[7]

The American advisors were thus faced with a cadre of personnel whose training had to include the unlearning of bad habits concerning vaccine handling and the use of assembly points.

A WHO smallpox eradication advisor, a Czechoslovak national, had been first assigned to Mali in December 1965. The American staff developed a generally close personal and professional relationship with this individual. The Malian Director General of Health refused to accept any program organization advice from the American personnel with which the WHO advisor did not concur. When the Americans saw the need to personally investigate reported cases of smallpox, the WHO advisor preferred to leave that task to Malian health personnel in the field, and as a result, the Director General refused the Americans permission to leave the capital. It is likely that even in the absence of the WHO advisor, the Director General would have taken that course of action, since the Malian government placed stringent travel restrictions on Americans. Also, the Director General might have feared significant political risks for himself if he had given permission to USAID personnel to freely travel around the country. Eventually, the WHO advisor was withdrawn; the Director General of Health left the country to become Secretary-General of the OCCGE,

and the Malian government relented on its travel restrictions when faced with possible program suspension. A Malian physician, Ousmane Sow, was then appointed director of the Endemic Disease Service, and along with the new Director General of Health, Daouda Keita, established a close collegial relationship with the American team.[8] Both doctors had received Masters of Public Health degrees from the University of Montreal.

Smallpox in Mali, 1966–1970

During the twenty-nine-year period, 1940–1969, smallpox in Mali was characterized by epidemic peaks every five to seven years. Prior to 1966, the disease was endemic in most of the country, with the highest incidence rates in the Inland Delta of the Niger and in the southern part of the country. The former is a vast area of swamps and floodplains the size of Maine. It is inhabited by migrating fisherman and nomadic herdsmen. Although the 1962–1965 smallpox campaign had numerous deficiencies, it resulted in cases falling from 1,706 (1961) to 284 (1966).[9]

The pre-1967 mass vaccination strategy in which assembly points were used and the lack of subsequent maintenance programs produced specific nonimmune populations, including newborns, the elderly, nomads, and small children who did not go to assembly points.[10]

Epidemic investigations in 1967–1969 revealed that the disease was transmitted slowly and primarily in the dry season. The latter reflected increased population movements and human contacts. In closed communities with high levels of susceptibility, smallpox transmission was sustained for long periods of time. The overall mortality was a low 5.7 percent, and laboratory studies from outbreaks confirmed that the virus was variola minor.[11]

Measles in Mali, 1966–1970

The annual number of cases of measles reported in Mali in 1966–1970 ranged from ten thousand to forty thousand with a mortality of 15–20 percent. These statistics explain why West African health officials were far more interested in measles control than in smallpox eradication. Measles in Mali was primarily a disease of young children, with 85.4 percent of cases occurring between six months and two years of age.

The severity of measles in Mali and other countries in West Africa was in part due to such co-morbidities as marginal nutritional levels, intercurrent infections, and an unsanitary environment. Traditional beliefs and practices also contributed to measles morbidity and mortality. For example, children sick with measles were often denied protein and hydration out of fear that they impeded the emergence of the rash. The emergence of the rash was viewed as important as it coincided with a diminution in severity of such other symptoms as myalgia, coryza, cough, fever, and photophobia. Such practices and others made children more susceptible to the complications of the disease.[12]

Contrasting Perceptions of Smallpox and Measles in Mali

Malian public health officials viewed measles as a far more serious problem than smallpox. The perception was understandable given the much higher incidence of measles and its high mortality rate. Smallpox, on the other hand, was viewed as a far less serious public health problem. Yet, the overriding priority of the USAID/CDC smallpox eradication/measles control program in

the nineteen participating countries of West Africa was smallpox eradication.

Malian health officials tried to structure a mass immunization program in response to reported measles morbidity. USAID personnel, on the other hand, fostered a strategy that gave the priority to smallpox eradication. The latter strategy did not lessen overall success in controlling measles, given the available resources.

The Beginning of the Mass Immunization Campaign

Six mobile teams of vaccinators and male nurses were initially trained by the American advisors. Eventually, several more teams were established and traveled to villages and nomad camps in Dodge trucks.

During the first half of 1967, the central region of Bamako was vaccinated. A total of 384,000 smallpox vaccinations were given, and 115,000 children between six months and six years were immunized against measles. That campaign, launched shortly after the arrival of the American advisors, reflected the principal focus of Malian health officials on measles control.[13]

While the campaign was under way, the American personnel began investigating smallpox outbreaks. By the spring of 1967, it was clear that most cases were occurring in the Inland Delta of the Niger and adjacent areas through which nomadic Peul herdsmen moved with their cattle. That area of Mali covered four administrative regions, parts of which were inaccessible for several months because of seasonal flooding.

Driven by a desire to control measles, Malian health officials next planned to send vaccination teams to the western region of Kayes. There had been no major smallpox outbreaks in that area for a long time, however. Given the timing of Mali's rainy season (June through September), the Malians planned to begin this campaign in October.

Change to a Strategy of Eliminating Smallpox Foci

Early experiences with investigating smallpox epidemics in Mali and success in controlling them through intensified surveillance and vaccination convinced the American advisors of the need to change the mass campaign strategy. It made no sense to them to have mobile teams giving smallpox vaccinations in smallpox-free areas of the country while outbreaks were occurring elsewhere. The American advisors proposed that the next dry-season mass vaccination campaign be launched in the Mopti region and the adjacent districts of the Segou and Sikasso regions corresponding to the zone where most smallpox cases were occurring.

Malian health officials were cool to the suggestion. The Director General of Health repeatedly said, "Measles is knocking on the door of the Kayes region." He thus was making a case for a measles-control-driven strategy. Also, the Kayes region was remote and poorly served by public services. Malians saw obvious political advantages in a mass immunization campaign against measles in a region that had received litle from the central government since independence.[14]

The American advisors kept pressing their case through the spring of 1967. As part of their effort, they invited Dr. George I. Lythcott, director of the regional office of the CDC West African Smallpox Eradication/Measles Control Program, to come from Lagos, Nigeria, to Mali. On April 19 he and the American advisors set off on an extensive ten-day trip through the smallpox endemic area of the Inland Delta of the Niger. They were accompanied by Dr. Benitieni Fofana, chief of the Nutrition Division

A Vaccination team poses in Mali, 1967: (standing, left to right) *Dr. Jiri Nedvideck (WHO advisor), Zahn Sabaker Traore, Sandiougou Dembele, Jean Paul Lastouillas (French cooperation advisor), Aliou Ballo; and* (kneeling, left to right) *Seydou Camara, Author, Bama Cisse, and Khalifa Dembele.*

of the Ministry of Health. Fofana (who later became Minister of Health) was one of the country's leading physicians. His opinions were highly respected by the Malian government. The team met with local administrative and health officials, investigated smallpox cases, and spoke with personnel of the Veterinary Service who knew the movements of nomadic groups.

Malian public health officials, who had previously made travel outside the capital difficult, readily consented to the trip. Their intent was to allow the Americans to see first-hand how difficult it would be to launch the proposed campaign. They said that to chart the movements of the nomads and migrating fishermen on the Niger River and arrange for the transportation of vaccinators by canoe, camel, and horse would require at least a year for planning alone.

After a grueling trip through the Inland Delta of the Niger, the American advisors were firmly convinced of the necessity of launching a campaign aimed at eliminating smallpox foci at the beginning of the next dry season in October 1967. The Director General of Health resisted, on the grounds that such a campaign required much more planning time. Conversely, however, he and other government officials also saw a year's delay as enabling them to deliver measles vaccinations to the Kayes region.

Fofana and Lythcott threw their considerable influence behind the October campaign. Eventually, the Director General of Health agreed. In October, after several months of

Jay S. Friedman (left) trains vaccinators in the use of the Ped-O-Jet injector, 1967.

meticulous planning, eight teams of vaccinators were sent into the Inland Delta of the Niger. The teams had to cover 150,000 square miles of cliffs, sand dunes, plains, and swamps; they planned to enter three thousand villages and more than one thousand nomad camps in order to conduct a monumental vaccination of a quarter of Mali's population: 1,500,000 people against smallpox, 300,000 children against measles, and 600,000 people against yellow fever. The campaign had to be completed within nine months, before the June rains. A similar but smaller smallpox containment vaccination program was conducted in the Gao region in the circle of Ansongo.[15]

Development of the E^2 Strategy of Eliminating Smallpox Foci

By June, the eight teams had delivered 1,425,560 smallpox vaccinations. Surveillance for smallpox was greatly improved, and outbreaks had been investigated and contained. Outbreak investigations, increased surveillance, and targeted vaccinations resulted in a quick interruption of transmission that routine mass immunizations could not have achieved. The strategy

of epidemiologic control of smallpox launched in Mali in 1967 eliminated the disease by 1969. This strategy was successful primarily because it was directed at those who had the disease and those who were most likely to get it.

As the Malian vaccination campaign was ending in June 1968, Dr. J. Donald Millar, the director of the CDC smallpox program, introduced a plan for eradication at a regional meeting in Abidjan, Ivory Coast. Developed by Dr. William H. Foege, who was then working in Nigeria, the plan included active surveillance, outbreak investigations, outbreak control, and rapid communication of disease intelligence.[16]

Known as E^2, the plan differed from the basic 1967–1968 Malian effort in that it included active surveillance (as opposed to the passive receipt of notification) and rapid communication of disease intelligence. E^2 was adopted in late 1968 by Mali and seven other West African countries where smallpox was still present.

Outcome of the Smallpox Eradication Program

By June of 1970, 4,170,608 smallpox vaccinations had been given in the attack phase of the program. This represented better than 90 percent coverage of Mali's estimated population. The last case of smallpox was detected in 1969. Thus, smallpox was effectively eliminated from Mali in three years.

Following the attack phase of the program, maintenance vaccinations were administered to children so as to prevent the buildup of a nonimmune population.

Outcome of the Measles Control Effort

While public health specialists believed that smallpox could be eradicated in Mali, no one held the same view with regard to measles. The reasons had to do with technological and population concerns. For measles, the best hope was control. Although measles vaccine could be delivered by automatic jet injector, it was much less heat-stable than smallpox vaccine. Even minimal levels of mishandling in the field and a breakdown in cold-chain storage resulted in inactivated vaccine.

Of greater significance were the high birthrates in Mali and other West African countries that created a fast-growing pool of susceptible children. Measles became highly endemic and communicable in such a large populations of susceptible children. (Smallpox, on the other hand, had a lower level of endemicity and communicability; it spread slowly in Mali, even amid large populations of susceptibles.)

The eradication of measles in Mali and Africa in general would have required intense ongoing immunization programs aimed at protecting susceptibles. Outbreak investigations, active surveillance, and rapid communication of disease intelligence—as were used in the eradication escalation program for smallpox—would also have been necessary. However, the strategy of the smallpox eradication/measles control program was largely driven by the desire to eradicate smallpox. Measles control was, in a sense, grafted onto that objective.

Contrasting Outcomes

The two outcomes of the program—smallpox eradication and measles control—stand in sharp contrast to one another. The relatively lower level of endemicity and communicability of smallpox certainly facilitated quick interruption of transmission. Conversely, the high endemicity and communicability of measles sharply challenged efforts to interrupt its transmission. While most people immunized against measles in

Mali in 1967–1971 were protected against the disease, high communicability and the quick build-up of large pools of susceptibles because of the high birthrates made it impossible to eradicate the disease with the resources then available.

Conclusion

Smallpox was quickly eradicated in Mali by 1969 through a strategy of eliminating foci of the disease and mass vaccinations. The low level of communicability of the disease facilitated the success of this strategy. Measles, on the other hand, was only controlled, and then but for a brief period of time. The high Malian birthrate quickly established large pools of susceptible children. The successful long-term control of measles or even its eradication would have required much more intensive and ongoing immunization programs. These programs would have had to regularly reach the vast majority of susceptible children.

♦

Notes

1. F. Fenner et al., *Smallpox and Its Eradication* (Geneva: World Health Organization, 1988), 1066–67, ix.
2. Ibid., vii.
3. Horace G. Ogden, *CDC and the Smallpox Crusade* (Atlanta: Center for Disease Control, U.S. Department of Health and Human Services, 1987), 21–35.
4. Fenner, *Smallpox*, 860.
5. Pascal J. Imperato, *Mali: A Search for Direction* (Boulder, Colo.: Westview Press, 1989), 1–13.
6. Ibid., 102–3.
7. "Smallpox Eradication Programme Report to the Director-General," *Official Records of the World Health Organization* 143, Annex 19 (1965): 161–75.
8. Fenner, *Smallpox*, 893–94.
9. "Smallpox Eradication Programme ," 161–75.
10. Pascal J. Imperato, Ousmane Sow, and Benitieni Fofana, "The Epidemiology of Smallpox in the Republic of Mali," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 66 (1972): 176–82.
11. Ibid.
12. D. C. Morley, "Measles and Measles Vaccine in Pre-Industrial Countries," *Modern Trends in Medical Serology*, ed R. B. Health and A. P. Waterson (London: Butterworths, 1963), 141; Pascal J. Imperato, "Traditional Attitudes towards Measles in the Republic of Mali," *Transactions of the Royal Society of Tropical Medicine and Hygiene* 63 (1969): 768–80.
13. Pascal J. Imperato, *A Wind in Africa: A Story of Modern Medicine in Mali* (St. Louis: Warren H. Green, 1975), 349.
14. Personal communication to the author by the Director General of Health, Bamako, Mali, 1967.
15. Pascal J. Imperato, Benitieni Fofana, and Ousmane Sow, "Stratégie et tactique pour la vaccination des populations du delta intérieur du Niger," *Afrique Medicale* 14 (1975): 307–16; Pascal J. Imperato, *An Outline to the Movements of the Pastoral Peul and the Migratory Bozo Fishermen in the Inland Delta of the Niger* (Atlanta, Ga.: U.S. Department of Health, Education, and Welfare, 1969).
16. W. H. Foege, J. D. Millar, and J. M. Lane, "Selective Epidemiologic Control in Smallpox Eradication," *American Journal of Epidemiology* 94 (1971): 311–15.

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